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Wilder Penfield and Brenda Milner

Encephalography by the Displacement Technique

*Dewey A. Nelson, William H. Jeffreys,
Robert H. Leaming, and
Fletcher McDowell*

Loss of Consciousness and Convulsions with Congenital Heart Disease

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Arthur Kling and Paul J. Hutt

Interrelations of Mesial Temporal and Orbital Frontal Areas of Man Revealed by Strychnine Spikes

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Psychiatric Problems of a Rapidly Growing Suburb

*Richard E. Gordon and
Katherine K. Gordon*

Autonomic and Adrenal Responsivity in Psychiatric Patients

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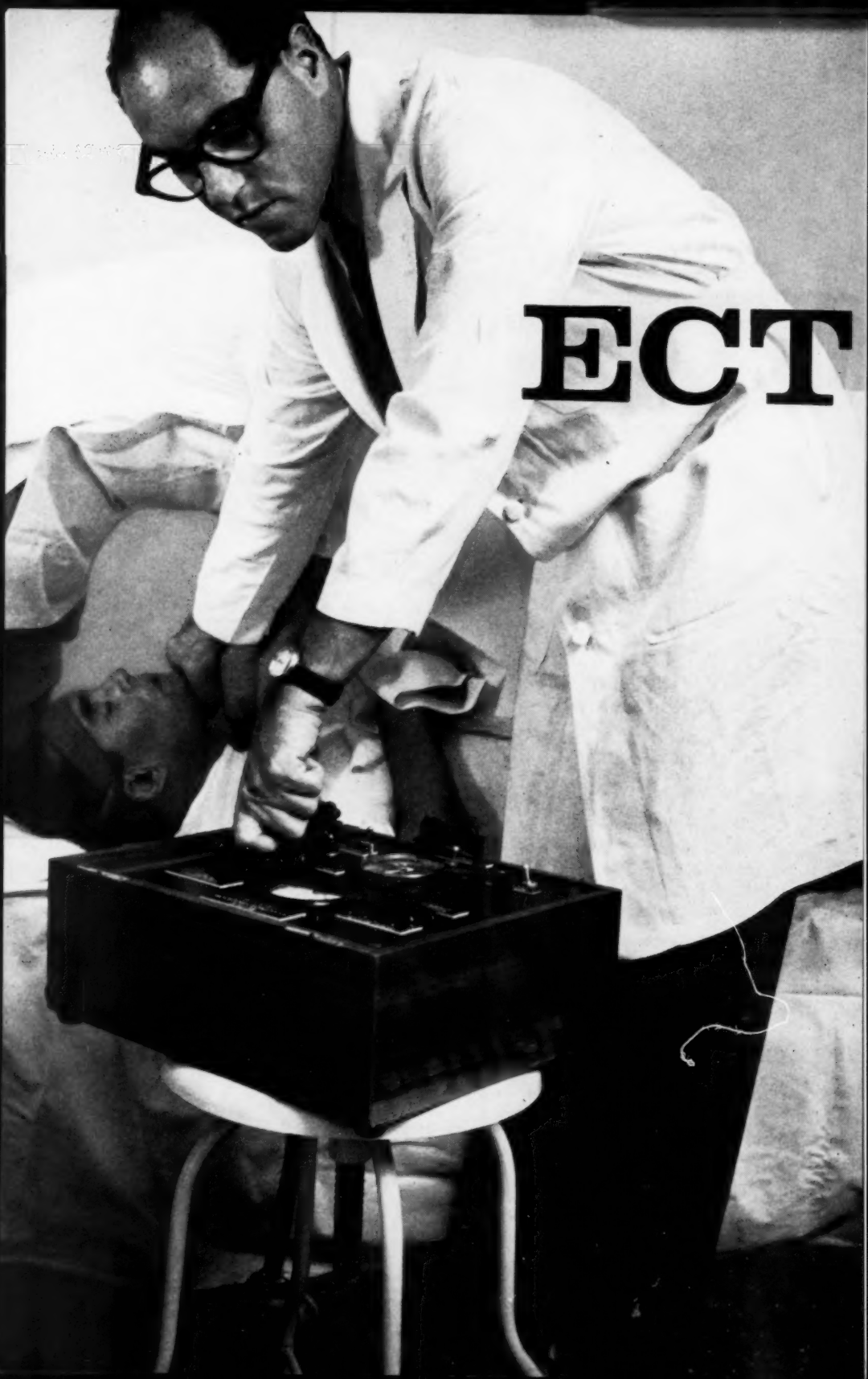


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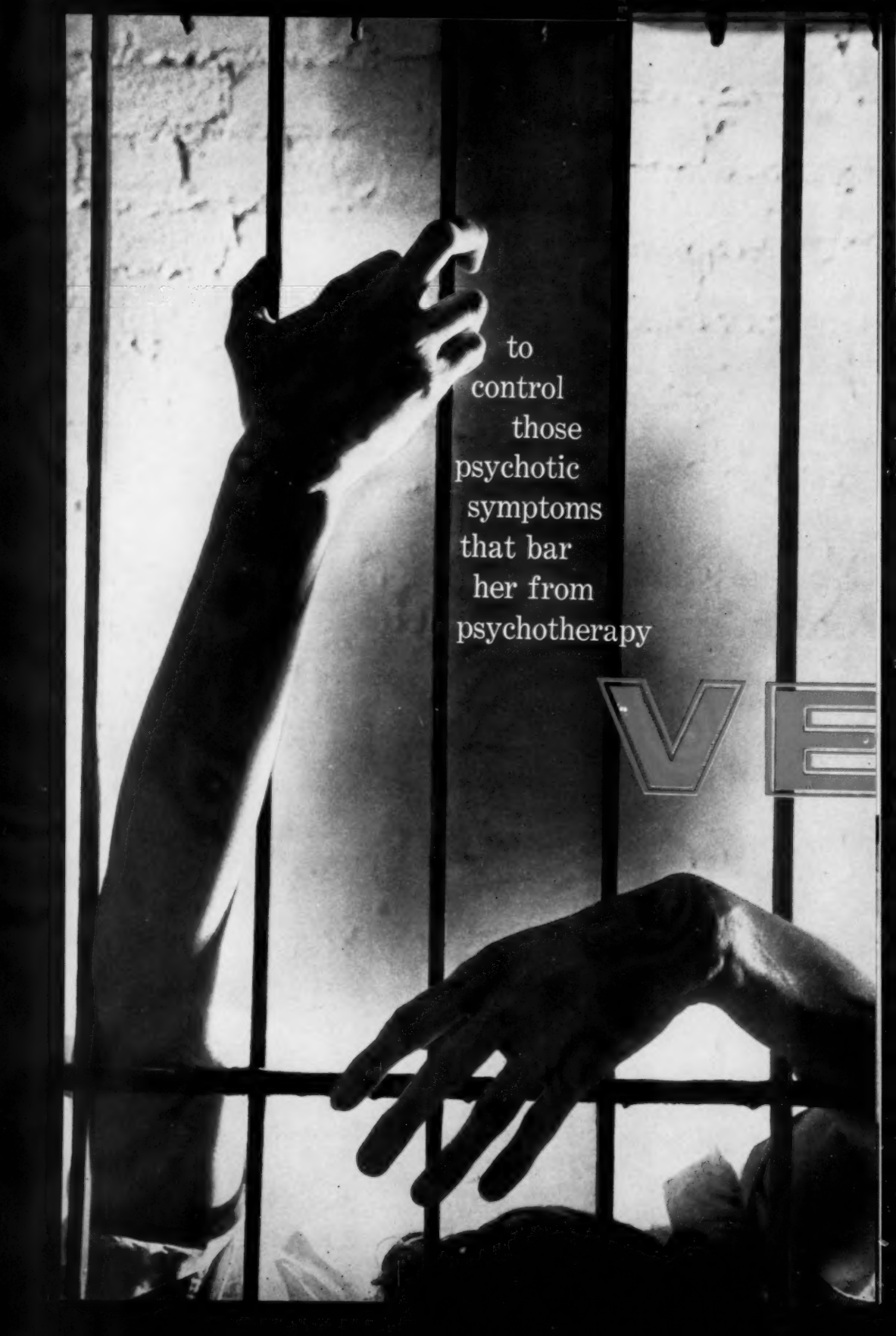
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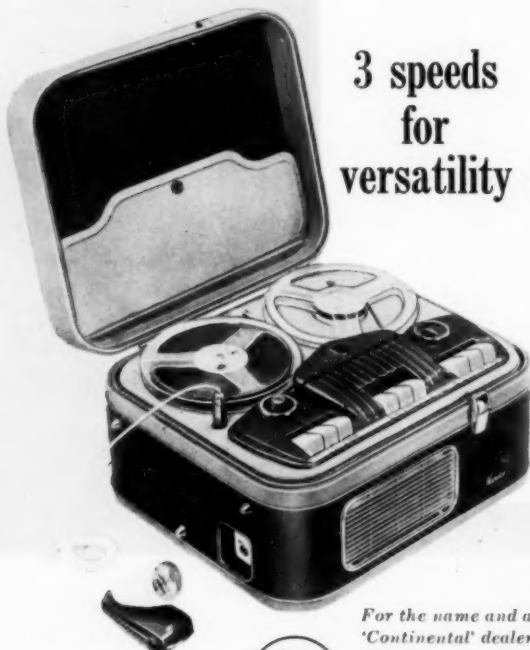


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Idiopathic epilepsy	11	—	6	38%	10	—
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SECTION ON NEUROLOGY

Memory Deficit Produced by Bilateral Lesions in the Hippocampal Zone

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It has often been assumed that memory depends upon the total action of the brain rather than upon some specialized intracerebral neuron mechanism. There is recent evidence, however, in support of the view that the recording of experience is localizable in the same sense that sensory functions and speech functions are localizable. Obviously, none of these subdivisions is separable from the work of the brain as a whole.

The following study shows that the capacity to record the daily current of conscious experience may be lost when there is bilateral destruction of a man's hippocampus and hippocampal gyrus. Functional paralysis of this recording mechanism does not, however, interfere with the patient's intellectual performance in other psychological tests not dependent on recent memory. Skills, language, and all those things which have already been learned are not lost.

This inability to record new experience is not found in cases of strictly unilateral destruction of the hippocampal zone. Unilateral partial temporal lobectomy, including the hippocampus and hippocampal gyrus, as

well as the uncus and amygdaloid nucleus, constitutes a reasonably successful method of treating focal epilepsy due to a unilateral epileptogenic lesion; and this operation does not cause any serious psychological impairment, provided the opposite temporal lobe is functioning normally. When the operation results in cessation of seizures, there is often a marked improvement in the patient's behavior, and there may even be an increase in general intellectual efficiency. The operation is usually followed by upper quadrant homonymous hemianopsia, but by no other neurological deficit.

Careful psychological testing of over 90 cases has in fact shown certain minor defects, which vary in type depending on whether the operation is carried out in the dominant or the nondominant hemisphere. These differences will be reported fully in a later communication. However, we should like to point out here that these unilateral operations do not normally cause a generalized memory disturbance, although with lesions of the dominant temporal lobe there may be a difficulty in learning and retention which is specific to verbal material but is dissociable from aphasia. In contrast to this mild and specifically verbal difficulty, two cases are reported herein in which a similar unilateral operation resulted in a grave, unexpected, and generalized loss of recent memory from which subsequent recovery has been but slight. It so happens

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that in both cases the operation was in the dominant (left) hemisphere, but there was also evidence of damage to the opposite temporal lobe. In both cases the hippocampus and hippocampal gyrus on the left were excised.

We believe these cases to be important, first, because the memory loss clearly followed a definite surgical removal, and, second, because it appeared in isolation from any disturbance of reasoning, attention, or concentration (as the psychological data will show). New light is thus shed on certain physiological mechanisms of memory, which will be amplified in the discussion by consideration of the disturbances of memory recording that are produced by local epileptic discharges and by electrical stimulations in the area of temporal lobe under consideration.

Furthermore, we place these cases on record as a warning, to neurosurgeons, of an unsuspected danger in the operation of complete removal of the inferior mesial border of one temporal lobe, the hippocampal zone, when there exists a lesion of the same zone in the opposite hemisphere.

Report of Cases

CASE 1.—*Memory loss after partial left temporal lobectomy.*

History.—Patient A., a 28-year-old glove cutter, was admitted to the Montreal Neurological Institute on Oct. 9, 1952, with a history of recurrent seizures since the age of 12 years, which had been increasing in frequency and severity despite treatment by various anticonvulsant drugs. His birth was thought to have been normal; but he had had one convulsive seizure at the age of 5 years. Otherwise, his early childhood had been uneventful.

Seizure Pattern.—The attack began with a sensation in the head (cephalic aura). He also described a feeling of "fogginess" and of being "about to leave this world." At times, this was accompanied by a cold sensation, when actual goose pimples were observed, and, more rarely, by palpitation.

Following this there was a period of "automatism," for which he would have no subsequent recollection. During this period the patient might drag himself across the floor in a sitting position. He fumbled with his clothes, humming and swal-

lowing. Finally he might seem to conduct himself in a normal manner, and in this final stage he seemed to lack only the capacity to make a permanent memory record of the passing stream of experience. For example, once, after an attack while at work, he cut several gloves but later did not recall having done so, although they had been cut accurately and well.

Preoperative Memory.—This patient complained of being forgetful, but this initial defect was clearly a mild one compared with the severe memory loss which was to follow his operation. Before the operation he could easily remember day-to-day happenings and recognize people, objects, and places as familiar. He had completed his high-school course successfully, despite being handicapped in English and history by poor verbal memory. He had always done well in mathematics, although he found it difficult to memorize formulae. Mechanical problems interested him greatly, and he enjoyed repairing machines, such as tractors. He stated, however, that he could not reassemble a machine that he had taken apart for repair unless he had a manual to follow, as he could not remember the relative positions of the various parts. The patient added that he believed his memory had deteriorated with increasing frequency of seizures and, conversely, that whenever there was a prolonged period without seizures his memory improved in all respects. Latterly he had given up reading books or magazines because he found it frustrating to remember so little of the contents.

Physical Examination.—Nothing definitely abnormal was found, although there was a questionable left facial weakness. He used his right hand for writing and glove cutting, but threw a ball with his left hand and claimed to be ambidextrous.

Radiological Findings.—The plain films of the skull showed slight flattening of the left side of the vault and very slight elevation of the floors of the anterior and middle fossae on the left. The pneumoencephalogram showed the ventricles to be of normal size, but all parts of the left lateral ventricle were very slightly wider than the corresponding parts on the right. Our radiological associate, Dr. Donald McRae, concluded from these findings that there was slight relative smallness of the left cerebral hemisphere, dating from birth or infancy.

Electroencephalographic Findings.—Because of the initial difficulty in localizing a focal epileptogenic area, numerous electroencephalograms were recorded. These studies were eventually summarized by Dr. Herbert Jasper as follows:

"Initial records suggested only bilaterally synchronous 3-per-second activity from the frontal regions. Later examinations, with pharyngeal electrodes, gave evidence of focal epileptic activity in

MEMORY DEFICIT DUE TO BILATERAL HIPPOCAMPAL LESIONS

TABLE 1 (Case 1A).—*Test Scores Before and After Operation and in Follow-Up Studies*

Test	Preoperative Examination (10/20/52)	Postoperative Examinations			
		11/14/52*	4/28/53	5/26/54	6/20/55
Wechsler Intelligence Scale	Form I	Form II	Form I	Form I	Form I
Full-scale I. Q.	106	88	104	107	109
Verbal I. Q.	102	80	102	107	103
Performance I. Q.	109	100	105	106	115
Subtests (weighted scores)					
Information	11	5	7	8	8
Comprehension	7	6	11	11	11
Similarities	11	5	8	10	8
Digit Span	7	6	10	11	7
Arithmetic	13	9	13	11	15
Picture Completion	8	5	6	9	12
Picture Arrangement	14	14	14	13	15
Block Design	14	13	12	13	10
Object Assembly	11	9	11	11	12
McGill Picture Anomaly	22/34	16/34	17/34	16/34	17/34
McGill Triangular Blocks	10/13	10/13	Not done	Not done	Not done
Benton Visual Retention	5/7	2/7	Not done	3/7	3/7
Wechsler Memory Scale					
Memory Quotient	94	Incomplete	72	72	75

* Patient aphasic at this time.

the pharyngeal regions, maximum on the left side but with some continuing abnormality also on the right. A clinical attack, which was recorded, gave clear evidence of initial discharge in the left pharyngeal electrode, but it spread very rapidly (in 15 to 20 seconds), producing high-voltage waves in a parasagittal area. In another seizure, this time induced by pentylenetetrazol U. S. P. (Metrazol), taken without pharyngeal-electrode recording, the onset seemed to be bilateral; first maximum right and then left, with a suppressor-like beginning for the main portion of the attack, leaving the focus of onset in doubt. It was concluded that there might be a local epileptogenic area in the left temporal region, but that the ease with which bilateral disturbances appeared must indicate a more general epileptic tendency, and possibly some bitemporal disturbance or a centrencephalic one, in addition to the left temporal area."

Since it seemed evident from these studies that most of the attacks originated in the left temporal region, and that there was little hope of controlling them by conservative medical therapy, it was decided to carry out a left temporal craniotomy in the hope of removing the initiating cause of attacks. This will be described below.

Preoperative Psychological Examination (Oct. 20, 1952).—The patient was a rather anxious young man of average intelligence who used words awkwardly and who showed an impairment of verbal recall, such is frequently seen in epileptogenic lesions of the dominant temporal lobe. He achieved a full-scale I. Q. rating of 106 on Form I of the Wechsler Intelligence Scale. The verbal I. Q. rating was 102 and the performance I. Q. rating 109. Detailed scores for the various Wechsler sub-

tests and for the other tests of the battery are shown in Table 1. It will be noted that the patient did well on tests requiring spatial ability, such as the McGill Triangular Blocks test and the Object Assembly and Block Design subtests of the Wechsler Scale. This presumably accords well with his trade of glove cutting. On the other hand, he obtained lower than average scores on the McGill Picture Anomaly Series and the Wechsler Picture Arrangement subtest, both of which require the rapid comprehension of pictorial material. In our experience patients with temporal-lobe lesions have difficulty with such tasks,¹ and in the case of the Picture Anomaly test this is particularly true of the right, nondominant, temporal lobe.

Preoperative Tests of Recent Memory.—Verbal recall was studied by means of the Logical Memory and the Associate Learning subtests of the Wechsler Memory Scale,² and recall of simple geometrical forms, by means of the Benton Visual Retention test. On these last two tests A.'s preoperative scores were within normal limits, but his immediate reproductions of the two stories of the Logical Memory test fell far below the normal level, and one hour later he could recall only a fragment of the second story and nothing at all of the first. His versions of these two stories are given verbatim here, partly for purposes of comparison with his fragmentary postoperative versions of the same stories and partly because the preoperative versions themselves illustrate his initial difficulties in verbal recall rather vividly. The original stories are also reproduced for the convenience of the reader, the slanted lines indicating

scoring units. Half-credits were given for minor variations within a scoring unit.

Story I: "Anna Thompson/ of South/ Boston/ employed/ as a scrub woman/ in an office building/ reported/ at the City Hall/ Station/ that she had been held up/ on State Street/ the night before/ and robbed/ of fifteen dollars./ She had four/ little children./ the rent/ was due/ and they had not eaten/ for two days./ The officers/ touched by the woman's story/ made up a purse/ for her."

Story II: "The American/ liner/ New York/ struck a mine/ near Liverpool/ Monday/ evening./ In spite of a blinding/ snowstorm/ and darkness/ the sixty/ passengers including 18/ women/ were all rescued./ though the boats/ were tossed about/ like corks/ in the heavy sea./ They were brought into port/ the next day/ by a British/ steamer."

A.'s immediate reproductions of these two stories were as follows:

Story I: "This poor lady had four children. She was robbed of what money she had. She told a policeman, and when they knew she was poor they were sorry for her and made up some money so that they could buy her something to eat."

Story II: "The New York liner was struck by a mine. The liner had lifeboats on it, and they

were tossed about. The people on the ships got into the boats, and most of them were rescued. I guess they rescued themselves by getting into the boats; I don't remember hearing anyone rescued them."

In both these reproductions the precise names and quantities have disappeared and the stories have been considerably shortened. However, the main ideas are retained, although the patient's attention seems to have wandered toward the end of the second story. When he was asked after an hour's other testing what he remembered of the stories that had been read to him at the outset, all he could say was: "About that ship that blew up."

These objective findings are consistent with the patient's own complaint that he could remember little of what he read, and they show that he had a specifically verbal difficulty. But this preoperative examination provided no evidence of a more general memory impairment.

Operation (Oct. 21, 1952).—Left temporal osteoplastic craniotomy and partial temporal lobectomy.

Under local anesthesia, a curved incision was made and a temporal scalp flap turned down, followed by the bone flap, attached to the temporal muscle.⁸ When the dura was opened, the lateral aspect of the temporal lobe appeared more or less normal. But there was no Sylvian vein. Instead,

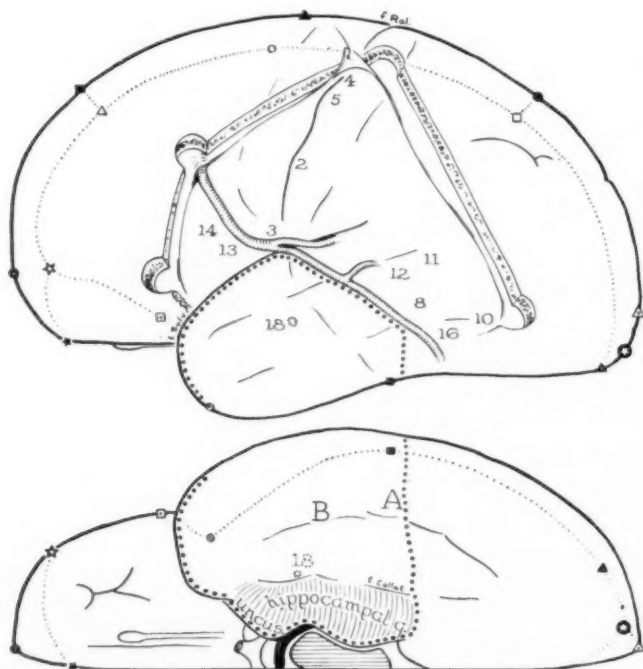


Fig. 1 (Case 1, A.).—Brain charts showing extent of left temporal lobectomy, broken line; hippocampal gyrus removed completely. The upper chart shows the mesial surface of the left hemisphere after brain stem and insula have been removed.

a large vein passed from the Sylvian fissure upward and forward over the frontal lobe, and the vein of Labbé slanted back farther posterior than usual over the temporal lobe.

The situation was studied carefully. Electro-corticography showed abnormal discharges recorded by the electrodes which had been placed underneath the temporal lobe at Points *A* and *B* (Fig. 1). A stimulating electrode, which was insulated except at the tip, was passed into the brain through the lateral surface at Point *18*. The tip of the electrode must have been near the uncus or hippocampus and so approximately in the amygdaloid nucleus. When a stimulating current was turned on, the patient said "nothing." The current was switched off, and an after-discharge was found to be present in the recording electrode placed at Point *B*. The electrographic discharge spread slowly forward and back to other electrodes. Meantime, the patient began to speak spontaneously: "I don't know," he said, "although he looks rodeo . . . rowdeum." He continued to speak, but the words now had no meaning that others could understand.

When the electrographic after-discharge ceased, it was obvious that he was again in normal contact with his surroundings, and he had no recollection of the period of strange speech.

It was concluded that there must be an epileptogenic zone of cortex in the inferior mesial portion of the temporal lobe and that the period of confusion and amnesia which stimulation had produced was an example of the attacks of automatism of which he had complained on admission, although the initial cephalic aura had not been produced.

In order to guard against postoperative aphasia, the cortex was explored for speech areas.* Electrical interference by stimulation at Points *8*, *11*, and *12* (also at Points *13* and *14*), while the patient was naming a series of objects, had caused the patient to become aphasic until the electrode was withdrawn. But similar electrical interference more anteriorly on the temporal cortex had no such effect. It was therefore considered that, although the excision would probably produce aphasia during the postoperative period of reactive edema, the aphasia would disappear in a week or two. No thought was given to the possibility of memory loss because of our previous experience with many similar removals, an example of which (Case 3) will be described below.

Excision.—It was decided to remove the anterior portion of the temporal lobe. During the process of removal marked abnormality was encountered in the region of the uncus and hippocampus. It was typical of epileptogenic tissue, the gray matter

being yellow and tough. A part of the hippocampal gyrus actually occupied a hollow in the lateral surface of the midbrain. This was the most abnormal portion of the sclerotic zone. It extended 1 cm. across the incisure of the tentorium into a little nest, where it would seem that it might have remained after the head compression, attendant on birth, was over. Such herniation sometimes occurs during birth^{8,9} and may produce an ischemic lesion of the hippocampal zone on either side or, no doubt, on both.

After removal of the anterior temporal lobe, including all of the uncus and hippocampal gyrus, a second electrocorticogram was carried out, which showed abnormal potentials of the epileptogenic variety still present in the inferior temporal frontier.

Further removal was carried out. The patient still named objects correctly. He seemed to have some difficulty with reading, but he had become sleepy and was difficult to arouse.

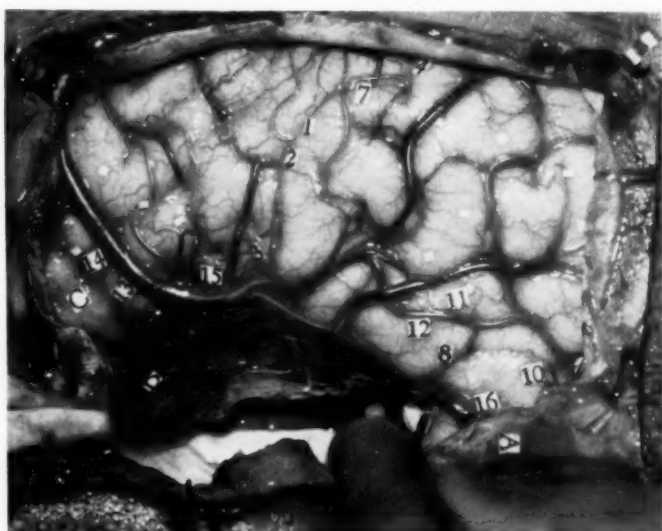
The final line of removal is shown by the dotted line in Figure 1, as well as in the operative photograph (Fig. 2). On the lateral surface it followed a fissure line, in which the vein of Labbé ran, then turned and ran perpendicularly to the base and across it to the brain stem (Fig. 1). As measured from the anterior wall of the temporal fossa, the line of ablation was 5.5 cm. along the fissure of Sylvius and 6.5 along the inferior temporal surface.

Early Postoperative Course.—After the operation the patient was aphasic for a time. By the end of the second week the aphasia was beginning to clear, although comprehension of speech was still noticeably impaired. At this time he remarked that words used repeatedly, such as "television," would suddenly regain their meaning after sounding quite strange. At the time of his discharge from hospital, 32 days after the operation, the aphasia was improving rapidly, and later it disappeared completely.

In addition to the aphasia, the patient showed marked confusion and disorientation; he failed to recognize the hospital staff and could not recall the events leading up to the operation. As the language difficulty lessened, it became increasingly apparent that there was a grave disturbance of recent memory. The psychological examination was carried out in two sessions, on successive days. On neither occasion did he recognize the examiner or the test materials. On the second occasion he remembered nothing of the previous day's tests, not even the fact of having been tested. The colored blocks that he had used the day before aroused no spark of recognition, and he was embarrassed at remembering so little of what was happening. At the same time it was clear that he could recall distant events quite well,

*This is the method of electrical interference employed by Penfield and Roberts⁴ to map out cortical speech areas.

Fig. 2 (Case 1, A).—Photograph of operation after anterior left temporal lobectomy. The insula is exposed by the removal. Tickets C and D are on the frontal and orbital opercula, respectively.



although he had a retrograde amnesia going back about four years.

The neurological examination revealed a right upper quadrant homonymous visual field defect, but was otherwise normal. Unfortunately, he had four small seizures while in hospital after operation. The first one was produced when all medication had been withdrawn and he was carrying out hyperventilation during electroencephalography. This postoperative electroencephalogram showed residual abnormality over the left frontal and right temporal regions, but the previous focus in the left pharyngeal region had apparently been removed.

Postoperative Psychological Examination (Nov. 14, 1952).—The psychological examination at this time showed the effects of the transient aphasia. Consequently, the Wechsler Verbal I. Q. rating fell from 102 to 80. However, there was no corresponding deficit on the performance tests of the Wechsler Scale, and spatial ability appeared to be as good as ever. But the score on the Picture Anomaly test (low before operation) fell markedly, and this additional perceptual impairment has persisted to the present time. This is a most unusual finding after a temporal lobectomy in the dominant hemisphere.

Formal verbal memory tests in this early postoperative period were, of course, affected by the aphasia. For this reason the results will not be described in detail here; very low scores were obtained. But A.'s postoperative inability to recall day-to-day happenings or to recognize objects and people, other than those he had known in the remote past, argues for more than a verbal defect. In fact, it was found that his ability to recall simple geometrical forms was also seriously im-

paired. The score on the Benton Visual Retention test had fallen from 5/7 to 2/7, the latter score being far below the normal range on this extremely simple test. This impairment, again, is a most unusual finding after dominant (left) temporal lobectomy (Case 3, below).

Follow-Up Studies.—This patient has returned to the Montreal Neurological Institute for three follow-up studies—in April, 1953; May, 1954, and June, 1955. He has had only minor attacks, and these infrequently. They appear to be well controlled by diphenylhydantoin (Dilantin). Nevertheless, the electroencephalogram of June 19, 1955, showed a very definite residual epileptogenic process. It was in the right anterior temporal region, the side opposite that of operation, and was strictly lateralized, with no recurrence of the abnormality on the left side. Our associate, Dr. Herbert Jasper, concluded that this was the continuation of the original contralateral abnormality seen (on the right side) in preoperative studies. He found no evidence of any generalized disturbance of cerebral activity and no widespread delta-wave abnormality, which would have been present if a major artery had been closed by operation.

The postoperative memory deficit has persisted, although there has been some slight improvement in recent months. But the patient retains his old skills. Furthermore, formal tests show his problem-solving ability to be unimpaired. He does his work as well as ever and seems to enjoy it. Nor has he forgotten how to behave socially. He appears to remember remote events clearly and can recall the names of the teachers and friends of his school days. However, there is still a retrograde amnesia

which, in the opinion of his family, covers the four years immediately preceding his operation. To illustrate this retrograde effect, his brother, who is a physician, pointed out that the patient was no longer able to recognize a girl who had been a close friend for the 18 months immediately before the operation.

The patient can recall very little of events subsequent to the operation, and formal tests of recent memory show extremely low scores, with negligible improvement to the present time. But the loss of recent memory is not absolute. Even in the first year after the operation he could remember a few things which interested him keenly, such as the times of the wrestling programs on television; and now he can recall a few of the outstanding incidents of the past year, such as being an usher at his brother's wedding in the autumn. But he cannot recount anything of the television programs he watches so assiduously, and he states that he cannot name or visualize any of the performers. This patient lives in Johnstown, N. Y., but he still thinks that Dewey (1942-1950) is governor of New York State, although he has learned that Eisenhower is President. Despite his keen interest in boxing, he believes that Dempsey (1919-1926) is still the heavyweight champion.

On his most recent admission to the Montreal Neurological Institute, in June, 1955, some improvement in memory was apparent to superficial examination. For example, two hours after supper he could still remember most of what he had eaten and could give a fairly accurate description of a doctor who had examined him earlier in the day. But gross defects were also apparent. Thus, he sat outside on the gallery the whole of one afternoon and was interviewed by one of us (B. M.) there; yet later that same day he denied ever having been on the gallery. Again, he appeared quite unable to learn the way to his bed. Such examples reveal a clear defect in recent memory, and one which is certainly not specific to verbal material.

Psychological Findings: The most striking feature of these follow-up examinations has been the contrast between the patient's good general intelligence and his loss of recent memory. The present I. Q. rating of 109 is slightly, but not significantly, higher than the preoperative level of 106, and there has evidently been complete recovery from the postoperative aphasia. It is particularly interesting that there has been no impairment of attention or concentration (as measured by digit repetition and mental arithmetic tests), a finding which contrasts markedly with the patient's inability to recall test material after a lapse of as little as five minutes if his attention has been diverted to something else in the meantime. The change of attention appears to be

crucial, since he can retain a three-figure number or an unfamiliar word association for many minutes, provided no distractions are introduced.

Formal Memory Tests: As in the early post-operative phase, so in these follow-up studies, formal testing has confirmed the clinical impression that the defect of recent memory is a general one. Thus, the immediate recall of the simple geometrical designs of the Wechsler Visual Reproduction test has remained fragmentary, though bearing some resemblance to the originals. The scores have been well below average and have failed to improve on successive follow-up examinations. The deficit is still more marked in delayed recall. There is also a difficulty in recognition after an interval, and not merely in recall. Thus, in April, 1953, on being shown six drawings, he obligingly "recognized" five of them, although in fact only three of them had been shown to him previously, half an hour before.

Although there was some impairment of verbal recall even before the operation, this is now much severer. Scores on the Associate Learning test two and one-half years after the operation show that A. is still unable to acquire new word associations within the limits of the testing situation, though on this particular test before operation his scores were within the normal range.

As before, the Logical Memory test still provides the most vivid illustration of this patient's memory difficulties. His versions of the stories read to him are given verbatim below.

April 28, 1953

Story I: "Anna Thompson. She robbed \$15. She had four children."

This is very fragmentary, and the sense is lost.

Story II: "They were brought into port by a steamer."

This is just an echoing of the last sentence of the story. The patient was then asked what he remembered of the previous story. He replied: "It seems to me you mentioned Anna Thompson. It was brought into the sea." This reproduction is very distorted, with fragments from the two stories run together. When he was asked one and one-half hours later what he remembered of the stories read to him, he looked blank and said: "Those stories? Nothing."

Let us compare this with the second follow-up examination, in May, 1954.

Story I: "Ann Thompson—had four children. She bought something for \$15."

Story II: "Sixty persons . . . on the . . . or was it 18? Did you say they got killed?"

Again, there was complete forgetting later.

In the most recent examination, in June, 1955, the following versions were obtained:

TABLE 2.—*Preoperative and Follow-Up Answers to Wechsler Information Subtest*

Question	1952	1954	1955
1. What is the capital of Japan?	Tokyo	I don't remember	I don't remember
2. Who invented the airplane?	Wright Brothers	Washington	Lincoln
3. What is the population of the U. S.?	137,000,000	2,365,000,000	300,000,000
4. Who wrote "Huckleberry Finn"?	Mark Twain	I don't know	I don't know
5. Where is Egypt?	Africa	Africa	Australia
6. What is the Vatican?	To do with the Pope	A name for Christ	I don't know

Story I: "Thompson had four children and got robbed of \$15 on the way somewhere."

Story II: "Eighteen women were rescued. It was brought in by a British steamer."

Although these versions are less distorted than the earlier ones, they are still mere fragments of the original stories. Moreover, immediately after retelling the second story, A. was unable to recall a word of the first, even with prompting.

The test was then repeated (i. e., the stories were read to him for a second time) to see whether there would be any improvement with practice. These second versions are given below, and it will be observed that they bear little relation to the first ones; so there is no evidence of improvement with practice within the limits of our testing.

Story I: "Anna—employed as scrub woman. Swept the floor. That was enough work for her."

Story II: "American liner struck by Liverpool and brought in by a steamer."

Although the crux of A.'s memory difficulty is in the recording of new impressions, it is perhaps worth pointing out that his previous store of knowledge has suffered some impairment. This is most apparent if we compare his answers to some of the questions of the Wechsler Information subtest in October, 1952 (before the operation), with his answers to the same questions in successive follow-up examinations (Table 2).

In summarizing this case, we may say that this is an instance of persistent memory difficulty resulting from partial ablation of the left temporal lobe, including the uncus, hippocampal gyrus, and hippocampus. We believe that the loss occurred because, in addition to the partial injury and the epileptogenic abnormality present in the left side, there was also a destructive lesion in the opposite temporal lobe. The electrographic evidence supports this view.

CASE 2†—*Memory loss after removal of hippocampal area.*

Automatism is discussed there also, from various points of view (see index).

(a) Left partial temporal lobectomy, 1946; (b) left complete excision of hippocampal zone, 1951.

History.—This patient, B, a civil engineer, was first admitted to Montreal Neurological Institute on Aug. 1, 1946. He was then 41 years old and had had recurring attacks of automatism for six years. He is said to have had one convulsion in infancy. At 25 years there was a head injury without loss of consciousness. It was said that he had a depressed skull fracture. But this was not borne out by our x-ray examination or by the findings at operation. At 35 he began to have momentary lapses in his conversation, first observed by his wife.

Seizure Pattern.—His attacks were ushered in by a sudden illusion of interpretation. The situation in which he found himself seemed suddenly "absurd," "silly." He would sometimes exclaim that things seemed queer. Occasionally he might also have a feeling of unreality. After that, his wife observed that he stared and became unresponsive. The unresponsive periods might last for several minutes, during which he behaved in an automatic manner, making fumbling movements with his hands and movements of mastication with his mouth.

Before such periods of automatism, and after the warning illusion, it was sometimes observed that his limbs were held stiff and his face grimaced. His head turned to the right. Toward the close of the attack, if at home, he would go out on the porch and look at the thermometer and barometer, then return to write down the readings in the record he was in the habit of keeping. This was a routine performance, for which he had no recollection.

Thus, there was postictal amnesia‡ for as long as 15 minutes. This began after the illusion of absurdity and included the transient stiffening of the limbs, the obvious confusion and fumbling, and the subsequent period when he carried out stereotyped activity that might appear normal to an onlooker. Toward the end of this period he could remember the readings of his instruments on the porch long enough to return into the house and write them down in his notebook. But he made no permanent memory record of this action, as demonstrated by his subsequent amnesia.

† The case of this patient is described in some detail by Penfield and Jasper⁶ (Case P. B., p. 508).

‡ The word ictus is taken to mean the period of active epileptic discharge. It is, of course, difficult to be sure how long discharge may continue and how long the subsequent fatigue of neurons is present after the discharge is over.

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No formal psychological examination was carried out during his first hospital admission. He made no complaint of general memory difficulty either before or after the first operation. His neurological examination was entirely negative before operation, and he showed only a partial upper quadrantic hemianopsia afterward. He has always been right-handed.

Radiological Findings.—A pneumoencephalogram, as interpreted by Dr. Donald McRae in July, 1946, suggested moderate diffuse cerebral and cerebellar atrophy but gave no evidence of a local brain lesion.

Electroencephalographic Findings.—The electroencephalogram of Aug. 5, 1946, pointed to a well-localized focal epileptogenic lesion of the left temporal lobe.

On the basis of the EEG findings, the pattern of the minor seizures, and the clinical evidence of a preponderance of right-sided movements in the convulsive phase of the seizures, it was concluded that the focus of origin of these attacks must be in the left temporal lobe.

He had no major convulsive seizures. The pattern of seizures pointed clearly to an origin of discharge in the temporal cortex of one side. The head turning to the right, which followed his initial staring expression, suggested origin in the left hemisphere, and the electroencephalogram pointed to discharge in the left temporal region.[§]

First Operation: Partial Temporal Lobectomy (Exclusive of Hippocampal Zone).—Under local anesthesia, a left temporal craniotomy was carried out on Aug. 14, 1946. When the dura was opened, a few scattered subdural adhesions were found, and there was moderate whitening of the arachnoidea, most marked in the anterior end of the fissure of Sylvius and over the first temporal convolution, which seemed narrow as it disappeared anteriorly into the temporal fossa.

There were electrographic abnormalities anteriorly over the temporal lobe, but stimulation did not reproduce the patient's attacks. The lobe was removed in its anterior 4 cm., but the removal was carried out on electrographic evidence alone. No

[§] We did not realize, in 1946, that temporal-lobe automatism was produced by discharge in the periamygdaloid region.⁷ It was also true that in 1946 we did not yet appreciate the importance of removing the hippocampal zone if one hoped to arrest seizures of this type by surgery. In the light of our subsequent experience, one would say that the illusion of absurdity was produced by discharge occurring in the cortex of the first temporal convolution adjacent to the uncus and that the staring and automatism made their appearance as the discharging state spread to the amygdaloid nucleus and hippocampal zone.

Penfield—Milner

true objective abnormality was found. The excision had been carried out as radically as was thought, at that time, to be safe in the dominant hemisphere, but the operation note expressed grave doubt as to the probable therapeutic success of this removal of the temporal pole.||

It was also not realized then what the limits of speech cortex in the temporal lobe might be and how far excisions could be carried without producing aphasia. There was then no proof that the hippocampectomy might not produce aphasia.

Postoperative Course.—The patient was speaking well at the end of the procedure, but about 24 hours later he became aphasic and confused. The aphasia reached its peak by the sixth postoperative day and began to improve soon afterward. The patient was discharged from hospital on the 29th day, at which time he was said to be only slightly aphasic. Electrographic studies made at this time still showed a sharp-wave discharging focus in the left inferior temporal region.

Second Admission.—The patient was readmitted to the hospital five years later, on Sept. 22, 1951, still complaining of seizures. But he was having attacks less often than before the operation, and the attacks themselves were shorter. The attack pattern had not changed greatly. There was automatism, but there was no longer any head turning. The patient stated that he often experienced feelings of unreality, which he described as "waves of peculiarity of things" or as "an inner feeling of out-of-this-world existence," "as though you were not the same person you were before." His aphasia had cleared up completely. On inquiry, he said that he had largely given up reading for pleasure.

Electroencephalographic Findings.—Dr. Herbert Jasper summarized the EEG evidence as follows: "Three successive examinations during this admission showed continuous slow waves from the left temporal region with occasional sharp waves and rhythmic 3-4 per second waves, without significant transmission for the most part to the right side, except during a Metrazol-induced seizure. During two such attacks the activity was definitely increased first on the left side with some spikes appearing, apparently from the mid-temporal region, which did not show transmission to the right. At the onset of the attack itself

|| Removal, alone, of cortex which is grossly normal rarely, if ever, brings about a satisfactory therapeutic result. Epileptogenic cortex is typically tough and often slightly yellow. At this time, in 1946, we had not yet realized that the hippocampal zone, since it is usually the most abnormal area, must be removed in most cases of temporal-lobe seizures if complete arrest of attacks is to be hoped for.

there was an initial period of low voltage, or "suppression," lasting six seconds, and then a 5 per second rhythm appeared from the right temporal region one second before the onset of high-voltage 2 per second waves from the left side. The succeeding portion of the discharge was maximum from the left side throughout. This is considered to indicate persistence of an epileptogenic focus in the left temporal region, the right being a reaction to the initial left-sided discharge during the attack."

Both the patient and his family were distressed by the persistence of his attacks. The attacks of automatic behavior threatened loss of employment. In view of the continuing electrographic abnormality in the left temporal region and the experience during the past five years that the left hippocampal zone could be removed with impunity, it was decided to perform a second left temporal craniotomy.

Before this operation a psychological study was carried out by one of us (B. M.), on Sept. 22, 1951.

Psychological Examination.—The patient was found to be of good intelligence, with numerical ability particularly well developed. He achieved a full-scale I. Q. rating of 119 on Form I of the Wechsler Intelligence Scale (Table 3). Certain salient features of the test pattern, which is not unlike that of Patient A., will be considered here.

First, the extremely high scores on both the Arithmetic and the Digit Span subtests of the

Wechsler Scale provide strong evidence against any disturbance of attention or concentration, and the fact that good scores were obtained on most of the verbal intelligence tests confirmed the clinical observation that there was no residual aphasia. Since at this time we did not have any reason to anticipate memory loss as a result of hippocampal excision, formal testing of verbal recall was not carried out before the operation. However, the recall of geometrical forms, as measured by the Benton Visual Retention test, was excellent. Also, at the end of the two-hour examination, the patient was able to recall details of the first tests given and referred to them spontaneously. It follows from this that there was no gross memory disturbance at this time.

An interesting feature of this first examination was the patient's poor performance on those visual tests which required the rapid comprehension of sketchily drawn pictures. Thus, his scores on the McGill Picture Anomaly Series and on the Wechsler Picture Arrangement subtest were below the average level and hence were quite poor for a man of superior intelligence. On these tests the patient was apt to be distracted by minor flaws in the drawings, while letting gross incongruities (such as the presence of a picture on the wall of a monkey's cage) pass unnoticed. His responses were also very slow. Patient A. had a similar visual difficulty, which we now know to be commoner in lesions of the right than of the left temporal lobe.

Second Operation: Removal of Uncus and Hippocampal Zone.—On Sept. 28, 1951, a second operation was carried out under local anesthesia. The bone flap was reflected again and the dura opened anteriorly over the empty portion of the middle fossa. We quote from the surgical record: "In the anterior part of the middle fossa, there were brown strands of what seemed to be fibrin or a very loose meshwork of connective tissue in the space left by the former removal. The insula was quite clear, and the large vessels (middle cerebral) could be seen passing over it. Some of the first temporal convolution passed around mesial and inferior to the insula and had not been removed. This was yellow, and as it passed backward into the uncus and hippocampus, there was objective yellowish abnormality.

"The electrographic abnormality seemed to be in the hippocampus. The ventricle was covered with a thin layer of ependyma. The electrodes were placed on the lateral wall of the ventricle, which collapsed, so that the electrodes were recording directly from the hippocampus."

The electrocorticogram recorded spike discharges from the hippocampus and hippocampal gyrus.

TABLE 3 (Case 2, B.).—Test Scores Before and After Second Operation

Test	Pre-operative Examination 9/22/51	Postoperative Examinations	
		23/10/51	17/5/56
Wechsler Intelligence Scale	Form I	Form II	Form II
Full-scale I. Q.	119	120	125
Verbal I. Q.	125	129	133
Performance I. Q.	110	107	111
Wechsler Subtests (weighted scores)			
Information	12	14	14
Similarities	9	8	13
Comprehension	12	14	13
Digit Span	17	16	16
Arithmetic	17	16	15
Picture Completion	9	9	11
Picture Arrangement	8	7	7
Block Design	11	11	10
Object Assembly	8	11	11
Digit Symbol	9	7	7
McGill Picture Anomaly	18/34	18/34	14/34
McGill Fourth Word	25/30	27/30	Not done
McGill Triangular Block	9/13	12/13	Not done
Stanford-Binet Vocabulary	31/50	35/50	Not done
Benton Visual Retention	6/7	3/7	5/7
Wechsler Memory Scale			
Memory Quotient	Incomplete	Incomplete	97

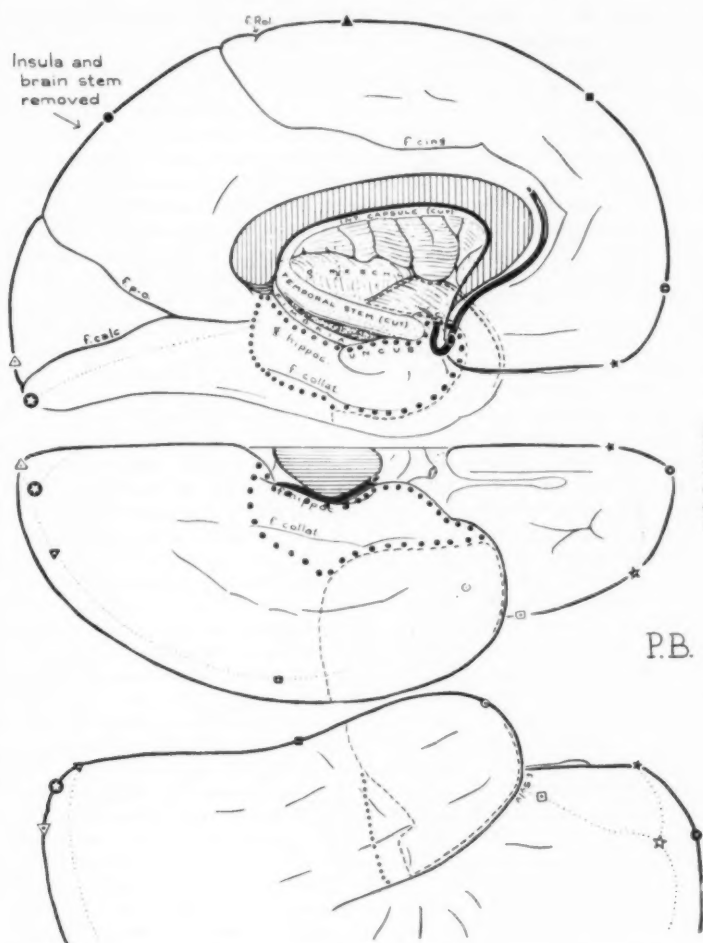


Fig. 3 (Case 2, B.).—First operation—excision indicated by broken line. Second operation—excision (uncus and hippocampal zone) outlined by dotted line.

P.B.

Local electrical stimulation produced a state similar to his attacks, and so the uncus and hippocampal zone of the temporal lobe were removed, as shown in Figure 3. Only a very small margin of tissue was removed from the lateral surface of the temporal lobe to leave a clean frontier of amputation.

Stimulation at a point which was on the hippocampus or hippocampal gyrus, or possibly uncus, caused him to say: "I felt a tremble over near the west side of the monument." After cessation of stimulation, he was asked where the monument was, and he replied: "On the road to Albany." Shortly afterward he had no recollection of the conversation. Our associate, Dr. William Feindel, who was observing the patient's responses closely, considered this episode to be a genuine period of confusion followed by true amnesia.

Early Postoperative Course.—This second operation was not followed by any aphasia. But, as in the case of A., it was soon clear that the patient's recent memory was disturbed. For example, three days after the operation B. did not remember who had operated on him or when the operation had taken place. Later he was able to identify one of us (W. P.) by name, but not the other members of the staff. The patient himself was aware of memory loss and made many jokes about it. On Oct. 11, nine days after the operation, he was able to remember for the first time what he had had for breakfast that same day. But he was never sure whether or not his wife had visited him on any given day, and questioning soon revealed that he was able to recall very little of what was happening around him. Moreover, his wife found evidence of retrograde amnesia, which she believed

went back to July 15, 1951, when B. had taken his daughter to register for a nursing course. Since then the patient's father-in-law had died and the patient himself had installed a new furnace in his house; but at first he had no recollection of either of these events, even when reminded of them by his wife. Later, he was able to recall visiting friends on Aug. 24, the night of his father-in-law's death; but there still appeared to be gaps in his memory for the period between July 15 and Aug. 24.

Psychological Examination (Oct. 23, 1951).—The most interesting feature of this postoperative examination was the contrast between the patient's memory defect and his other intellectual functions, which remained at their high preoperative level (Table 3). His I. Q. rating on Form II of the Wechsler test was now 120, as compared with 119 on Form I before the operation. The fact that some verbal tests, such as the Stanford-Binet Vocabulary and the Wechsler Comprehension tests, actually showed improvement (both in quality of response and in total score) emphasizes the complete absence of postoperative aphasia.

Tests of Recent Memory: As in the case of A., formal memory testing confirmed that the memory defect was a general one, affecting both verbal and nonverbal material. Impairment in the ability to reproduce visual patterns from memory is shown by the fact that the score on the Benton Visual Retention test had fallen from 6/7 to 3/7. As already noted, this is a very simple test of immediate retention, and few errors are made by the normal person. Again, when the patient was asked to draw a plan of his house and garden, with the surrounding landmarks, he made a 90-degree error in the position of the garage. Before the operation his plan had been meticulously exact and detailed. Verbal-memory testing also revealed striking defects. These can best be illustrated by giving verbatim B.'s versions of the two stories of the Wechsler Logical Memory test. The original stories are again reproduced for purposes of direct comparison.

Story I: Anna Thompson/ of South/ Boston/ employed/ as a scrub woman/ in an office building/ reported/ at the City Hall/ Station/ that she had been held up/on State Street/ the night before/ and robbed/ of fifteen dollars./ She had four/ little children/ the rent/ was due/ and they had not eaten/ for two days./ The officers/ touched by the woman's story/ made up a purse/ for her./

Story II: The American/ liner/ New York/ struck a mine/ near Liverpool/ Monday/ evening./ In spite of a blinding/ snowstorm/ and darkness/ the sixty/ passengers including 18/ women/ were all rescued./ though the boats/ were tossed about/ like corks/ in the heavy

sea./ They were brought into port/ the next day/ by a British/ steamer./

B.'s immediate reproduction of Story I was as follows:

"Anna X. reported to the officers that she had been robbed last night of several hundred dollars that was needed to pay for the sustenance of her children. They said that they would do what they could immediately to help her."

We see that, apart from the first name, which was favored by its position at the very beginning of the story, all the precise details of names, places, and quantities have been lost. However, the gist of the story has been retained. The exaggerations and the rather grandiose style were typical of the patient's speech at this time.

Story II was next read to the patient, who reproduced it as follows:

"The American liner 'New York' struck a mine near Liverpool in a blinding snowstorm. The people vainly attempted to be brought into port by boats, but great dismay was sustained."

This begins accurately and well, but after the first sentence the thread is lost and the story is completely distorted. An emotional note is introduced, which was lacking in the original.

The patient was then asked to repeat, without further delay, what he remembered of the first story. This he was totally unable to do, explaining that he had been "concentrating too heavily on the second one." He added that the effort to recall the first story "created terrible confusion and pandemonium."

On the Associate Learning test, which followed, he failed to master a single unfamiliar association. Here he would substitute habitual associations ("cabbage-vegetable" instead of "cabbage-pen") for the new associations the test required him to make. The normal person can forge some links between such unrelated words which make him able to associate them at least for the duration of the test, and sometimes for much longer; in B.'s case such new learning was apparently impossible, at least within the limits of our testing.

Upon completion of the Associate Learning test, which lasts only about five minutes, the patient was asked what he recalled of the previous test. He replied: "I think there were some other words that were easier." He did not even recall the fact that stories had been read to him, and subsequent prompting failed to elicit any of the content of these stories.

In summary, then, the psychological examination at this time revealed a selective disturbance of recent memory, with no corresponding impairment of attention, concentration, or reasoning ability. There was no suggestion of aphasia.

Later Postoperative Course.—Physical examination and neurological tests showed no change after

MEMORY DEFICIT DUE TO BILATERAL HIPPOCAMPAL LESIONS

operation. The patient returned home on Nov. 20, 1951.

The patient had had one or two brief attacks of automatism following operation, and an electroencephalogram taken on Oct. 20, 1951, had shown a few sporadic waves from the right temporal region, raising the question of abnormality on the side opposite the removal. No epileptiform disturbance was seen on the left side at this time.

Follow-Up Studies.—In December, 1951, three months after this second operation, the patient was seen by Dr. Lawrence Kubie in New York City, and was interviewed under amobarbital (Amytal) sodium in an attempt to recover some of the forgotten material. The results were entirely negative. He is said to have developed "a mildly euphoric, hypomanic, aggressive state with confabulations, not unlike that of a Korsakoff psychosis."

This patient, unfortunately, has continued to have about two attacks a month; these have consisted merely of short periods of confusion, except that he fell on one occasion. He has returned to the Montreal Neurological Institute three times for further study, twice in 1952 and, more recently, in May, 1956, four and a half years after the operation that had resulted in memory loss. During the last admission to the hospital the patient had a series of attacks of automatism after withdrawal of medication. One such spontaneous clinical attack was recorded electrographically, and was marked at the onset by a suppression of activity over the right temporal region, which then spread to involve the whole right hemisphere. This was followed by regular 4-per-second sharp waves, also from the right hemisphere, before appearing over the left temporal lobe. Dr. Herbert Jasper concluded that the patient's present attacks were arising from a deep-seated focus on the inferior surface of the right temporal lobe anteriorly, although between attacks the main abnormality was seen on the left side. These studies show that in this case, as in that of A., there is evidence of damage to the right, as well as the left, temporal lobe.

B.'s memory has improved appreciably during the four and a half years which have elapsed since operation, the main improvement occurring in the first year. But there is marked residual impairment. He has not been able to learn anything new in his work and has been demoted from the position of department manager to that of draughtsman, entirely on account of his memory difficulty. He cannot learn the names of new business associates, and if, for example, he is interrupted while telephoning, he will forget completely the substance of the telephone conversation. Yet he is still able to prepare very complicated blueprints, though tending to work more slowly than before.

This patient has always been interested in weather charts and keeps a graph of the maximum and minimum temperatures and pressures. Each morning he goes out on the gallery and reads the four values. He then comes back into the house and enters the readings on his graph a few seconds later. The severity of the initial memory defect is illustrated by the fact that when he first returned home, two months after the operation, he was unable to recall the four numbers at one time and so was forced to make two journeys. Later he found himself again able to recall all four numbers at one time.

B. claims that the loss of recent memory is most apparent in the early morning; upon waking, "everything seems blank," and he may not even know what month it is. He feels least confused in the evenings but even then is unable to join in any general conversation because he cannot understand allusions to current events. He has, therefore, been forced to relinquish his former interest in social and political affairs.

It is interesting that, despite these gross defects, B.'s memory loss has not been absolute, and this is true even for the early postoperative period. Thus he remembers receiving a very affectionate welcome from a close friend on his return home from Montreal in November, 1951; yet other events from that period appear to have been lost. At the present time he is able to give some account of outstanding occasions, such as his daughter's wedding, two years ago. He also knows the address of the house to which he recently moved and can describe its topographical position with reasonable accuracy. But for all small day-to-day events his memory remains grossly unreliable.

Psychological Findings: Informal examination of this patient during his last admission to the hospital, in May, 1956, showed clearly that his memory was still unreliable. Thus, one of us (B. M.) interviewed him late one afternoon in B.'s own room on the third floor; yet the next day B. stated that the interview had taken place in B. M.'s office on the first floor. He remembered nothing of the conversation and was uncertain whether it had taken place in the morning or in the afternoon.

Formal memory tests were administered in October, 1952, and again in May, 1956. Both examinations showed evidence of improvement as compared with the early postoperative period, but the scores in 1956 were no higher than in 1952, suggesting that the main improvement had occurred during the first year after the operation. The patient's general intelligence remains at a high level, with no deterioration during the last four years. His present I. Q. rating on Form II of the Wechsler Scale is 125.

Tests of Recent Memory, May, 1956: In this latest examination, B.'s immediate recall of the stories and drawings of the Wechsler Memory Scale was within dull normal limits, and he achieved a Memory Quotient of 94. This, of course, compares most unfavorably with the intelligence rating of 125, but represents a considerable improvement as compared with the scores for the early postoperative period. However, he was much less successful on tests of delayed recall. For example, after hearing the second story of the Logical Memory test, he was quite unable to recall anything of the first which had been read to him immediately before. Moreover, on repeated testing with the same material, he failed to show any improvement with practice, the Memory Quotient after the third administration of the test being actually a little lower than after the first administration.

It is apparent from B.'s vague descriptions of recent happenings that his memory difficulty continues to be general rather than specific for verbal material, and formal testing confirmed this. Thus, he was shown a cork and a bath plug and told to memorize these objects. Half an hour later he was unable to state what objects he had seen and, furthermore, was unable to select these objects from a group of others. Nor could he describe test material he had used the previous day, and when asked to do so, he would resort to confabulation. Thus he stated that he had had to fill in blank spaces in questionnaires and work out written mathematical problems involving the calculation of areas. None of this was so.

In summary, in this case removal of the hippocampal zone on the left, without postoperative aphasia, has resulted in a profound disturbance of recent memory. The removal was unilateral, but there is electrographic evidence pointing to an additional lesion in the corresponding area on the right side, and the patient has continued to have seizures which are clearly temporal in origin. This patient has shown more improvement than has A., but the memory defect is still severe enough to prevent a return to the administrative part of his former work.

Summary (Cases 1 and 2).—As we stated earlier, partial unilateral temporal lobectomy does not normally result in this generalized type of memory loss. Our conclusion in regard to these two cases is that there was, preoperatively in each, an unsuspected, but more or less completely destructive, lesion

of the right hippocampal zone. Although the left uncus and hippocampal area was epileptogenic, it must have been carrying on some normal function. In each case the surgeon found marked sclerosis produced by herniation of the inferior mesial temporal cortex at the time of birth.⁶ Such a mechanism may produce ischemic injury, which can be bilateral as well as unilateral. In both our cases the electrographic findings would favor a bilateral injury.

Typical Control Case.—The next case, that of C., is presented as a control study for purposes of comparison with our two cases of memory loss. This case has been chosen as a typical example from a long series of unilateral temporal lobectomies in the dominant hemisphere.⁸ The excision was just as extensive as in the cases reported above, but there was no evidence of damage to the opposite (right) temporal lobe and no memory loss.

CASE 3.—Control case (C.): partial left temporal lobectomy without memory loss.

History.—This 23-year-old bank clerk was referred by Dr. R. N. DeJong, of Ann Arbor, Mich., after a variety of medications had failed to control his seizures.

At age 10, after a mild attack of measles, he had had a series of convulsive seizures which continued for eight hours, until stopped by rectal anesthesia. From the age of 14 years he had had recurring seizures like those of which he complained on admission.

Seizure Pattern.—The sequence was as follows:

1. Bodily sensation. He would "feel different." He would say "yes" and then remember no more of the episode.

2. Staring and posturing, with slow turning of the head to the left and pulling of the face to the left; this would be followed by symmetrical licking movements.

3. Postictal aphasia.

Preoperative Examination.—Physical examination was negative. The patient was right-handed. Radiological study showed no asymmetry of the skull. Encephalography revealed the fact that the left lateral ventricle was a little larger than the right throughout.

Electroencephalography, as interpreted by Dr. Herbert Jasper, showed an area of continuous slow and sharp waves, best demonstrated when pharyngeal electrodes were used. "Phase reversals and sharp waves were obtained very consistently from the left of the two pharyngeal leads. There were

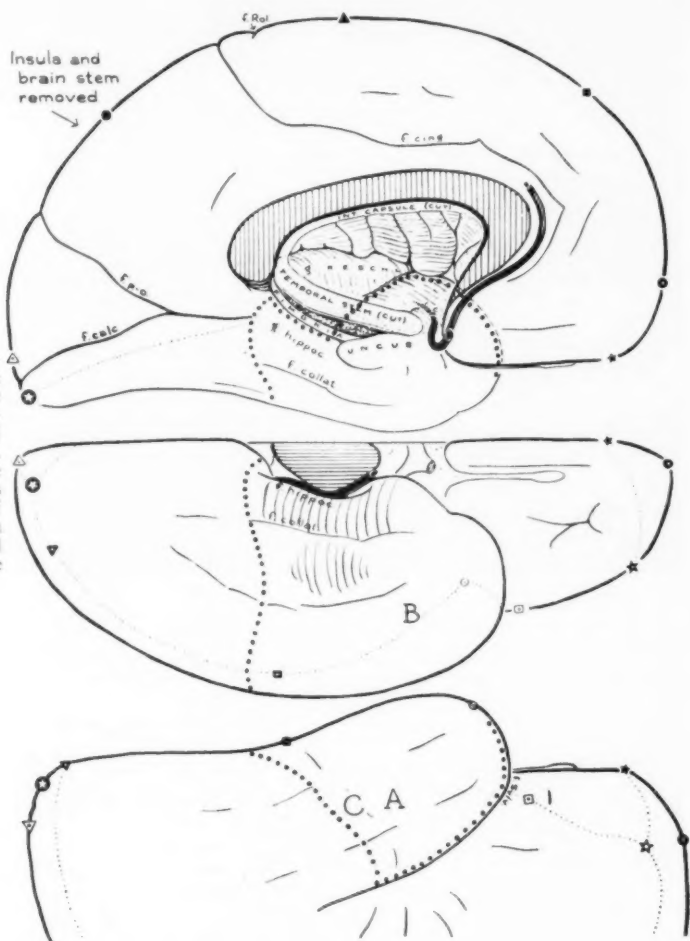


Fig. 4 (Case 3, C).—The dotted line shows the extent of removal of the left temporal lobe, including all of the hippocampal gyrus and hippocampus. Above, the mesial surface of the hemisphere is shown after removal of the insula and brain stem. Below, the lateral surface is shown, upside down.

only very occasional synchronous bilateral rhythmic waves, there being no independent discharges on the right side." These electrographic results were thought to be "consistent with a well-localized epileptogenic lesion of the left anterior and inferior temporal region." The clinical and radiological evidence supported this conclusion, and operation seemed justifiable.

Preoperative Psychological Examination (May 24, 1954).—This young man had graduated from junior college without difficulty, and formal testing showed him to be of superior intelligence. He achieved a full-scale I. Q. rating of 121 on Form I of the Wechsler test, and the two sections of the test were well balanced, the Verbal I. Q. being 119 and the Performance I. Q. 119 also. His comprehension of pictures was rapid and accurate, and in this respect he differed from Patients A.

and B., both of whom did poorly on the McGill Picture Anomaly and the Wechsler Picture Arrangement tests.

As with most patients with epileptogenic lesions of the dominant temporal lobe, there was a slight impairment of verbal recall, of which the patient himself complained. Thus, on both the Logical Memory and the Associate Learning tests of the Wechsler Memory Scale, C's scores were rather low, considering his youth and good intelligence. Scores on these tests were, however, within normal limits. In contrast to the slight verbal difficulty, there was perfect recall of the geometrical drawings of the Wechsler test, even one hour after their presentation.

Operation: Partial Left Temporal Lobectomy (May 27, 1954).—Left temporal osteoplastic craniotomy was carried out under local anesthesia. There

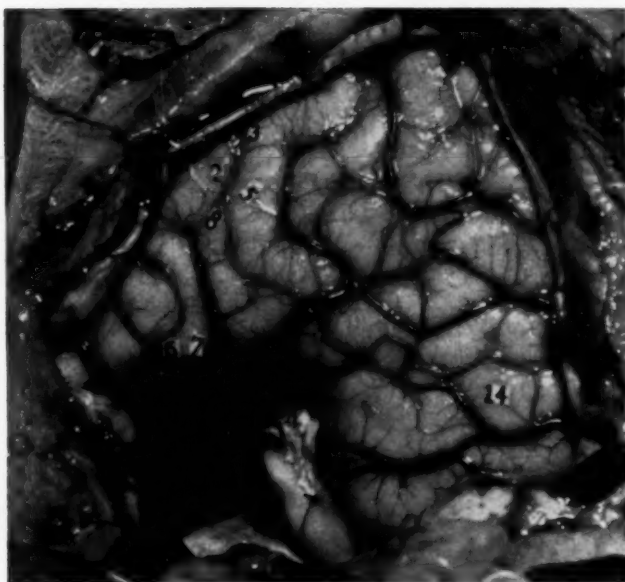


Fig. 5 (Case 3, C).—
Operation photograph.

were definite subdural adhesions in the vicinity of the fissure of Sylvius, suggesting that there had been a subdural hematoma in the distant past. The left temporal lobe appeared to be smaller than normal.

Electrocorticography showed definitely abnormal potentials from electrodes placed at *A*, *B*, and *C* in Figure 4. Stimulation failed to reproduce the warning of the patient's seizure. Electrical interference at Point 14 in Figure 5 caused the patient to become aphasic.

The anterior portion of the left temporal lobe was removed, going back 5 cm. along the lateral surface and 6.5 cm. along the base, as shown by the dotted line in Figure 4 and in the photograph (Fig. 5). There was gross abnormality of the cortex on the undersurface of the temporal lobe, and the hippocampal gyrus was quite tough. A portion of this gyrus was herniated over the edge of the incisura tentorii and had remained there, as in Case 1 (Fig. 1).

The most likely explanation seemed to be that brain compression, at the time of birth, had produced incisural herniation, resulting in sclerosis, and that, associated with this, there had been a subdural hematoma. The attack of measles at the age of 8 years must be looked upon as a precipitating agent in, rather than as the cause of, the fits.

The ablation included all of the hippocampus and hippocampal gyrus. The posterior portion of the insula was found to be abnormal electrocorticographically. This was removed also and

proved to be sclerotic. The end of the inferior horn of the ventricle, which had been cut across, was closed with a piece of absorbable gelatin sponge U. S. P. (Gelfoam), held in place with a silk suture passed through the ependymal walls, as shown in Figure 5. This closure is carried out by us routinely to prevent aseptic postoperative meningitis and fever.

Postoperative Course.—After operation, speech was normal for two days, after which the patient became aphasic and developed transient weakness of the contralateral lower part of the face. There was also some twitching of the right side of the face on the second and third postoperative days (neighborhood seizures). There was never any sign of memory difficulty as far as the daily happenings of the hospital were concerned, and he recognized the various members of the staff and could place them in the correct context. The electroencephalogram of June 11, 1954, showed some residual slow waves around the excision, above the fissure of Sylvius on the left side. No other abnormality was seen, and the epileptogenic "spike" zone in the left temporal lobe seemed to have been successfully removed.

Psychological Examination (June 21, 1954).—At this time there was still some residual language difficulty, and as a result the I. Q. level had fallen slightly (from 121, on Form I of the Wechsler test before the operation, to 114, on Form II after operation). Spatial ability and arithmetic remained at the high preoperative level.

Formal testing confirmed the clinical impression that there was no important memory loss. Particularly striking was the fact that the patient was able to reproduce perfectly three of the four geometrical drawings which had been shown to him on May 24, three days before the operation. Very few of our patients are able to do this, irrespective of the locus of the cortical excision. C. was also able to recall a few of the word associations he had learned before operation.

After operation new learning was tested by using Form II of the Wechsler Memory Scale, since Form I was already quite familiar to the patient. In this postoperative examination he again gave proof of his excellent memory for geometrical forms, obtaining full marks on the Visual Reproduction test. Verbal recall was less accurate than before, but the results are hard to interpret because the patient was still slightly aphasic. Thus, in attempting to reproduce stories that had been read to him, he would use a few stereotyped phrases over and over again, instead of giving the exact words of the original. Nevertheless, one and a half hours later he could still recall the gist of the stories without difficulty. He could also still recall three of the four drawings of the Visual Reproduction test and recognized the fourth one when it was shown to him again together with others which were unfamiliar. These results are in marked contrast to those obtained with A. and B. at a comparable stage after the operation, and we can conclude that C.'s memory functions were essentially intact.

Subsequent Course.—This patient has done well. He has had one seizure only, and that a year after operation, following a strenuous game of tennis. He has returned to full-time work in the bank and does not complain of increased memory difficulty. An electroencephalogram taken in May, 1955, a few days after his seizure, showed minor dysrhythmia in the left central region but no epileptiform activity. Physical examination was normal.

Further psychological studies at this time showed a return to the preoperative level on practically all the tests of the battery, though there was some reduction in word fluency. It is interesting that, with recovery from aphasia, scores on verbal memory tests had returned almost to the preoperative level, although they were still rather low for a person of superior intelligence. Visual memory remained excellent. Moreover, in contrast to our first two cases, C. could still recall some of the material, both verbal and nonverbal, from the postoperative memory tests he had taken nearly a year before.

Summary.—This case has been described to illustrate the negative effects of partial

unilateral temporal lobectomy, including the uncus, hippocampus, and hippocampal gyrus, when there is no evidence of damage to the opposite temporal lobe. In this patient removal of the epileptogenic area in the dominant (left) temporal lobe merely accentuated slightly the mild verbal-learning difficulty which had been present before operation, and at no time was there any general memory loss.

Summary

Unilateral partial temporal lobectomy, including usually the hippocampus and hippocampal gyrus, has proved an effective treatment for temporal lobe epilepsy in a considerable series of patients, and careful psychological testing before and after operation in over 80 such cases has failed to show any generalized memory loss. In two cases, however, this unilateral operation resulted in a grave, persistent, and totally unexpected loss of recent memory. In one of these cases the removal was carried out in two stages, separated by a five-year interval: The memory loss followed the second operation, at which time the uncus, hippocampus, and hippocampal gyrus alone were excised. In both patients the operations were in the dominant (left) hemisphere.

The present paper reports the psychological findings in these two cases (A. and B.), together with a typical control case (C.) showing no memory loss after a comparable removal also in the dominant hemisphere.

Our conclusion in regard to the two cases showing memory loss is that there was, preoperatively in each, an unsuspected, but more or less completely destructive, lesion of the right hippocampal zone and that the corresponding area on the left, though epileptogenic, must have been carrying on the normal function that is required of these areas. The operation would thus deprive the patient of hippocampal function on both sides.

This conclusion seems justifiable, since in each case the surgeon found marked sclerosis of the left hippocampal area, which we attribute to herniation of the inferior mesial temporal cortex through the incisura of the tentorium at birth. It is known that this mechanism can easily cause a bilateral injury. In each case there is now, after operation, continuing electrographic evidence of epileptiform activity in the corresponding area in the opposite (right) temporal lobe.

Review of Literature

There is some support in the clinical literature for the belief that a bilateral lesion of this inferior and mesial portion of the temporal lobe does interfere with memory in a specific manner.

In 1952 Glees and Griffith⁹ described a case of bilateral destruction of the hippocampus and of the hippocampal and fusiform gyri (presumably by vascular accident) in which disturbance of recent memory was an early and prominent symptom. Autopsy showed that only 25% of the fornix fibers remained intact, but the mammillary bodies appeared grossly normal, as did the rest of the brain. On the basis of this one case and an earlier, but even less conclusive, case reported by Grünthal,¹⁰ they suggested that in the adult the hippocampal formation was essential for the maintenance of recent memory and normal mental activity. (They introduced the qualification "adult," since Nathan and Smith¹¹ had failed to find any particular mental deficit in a patient who was born with partial agenesis of the hippocampal formation and fornix system.)

Clearer-cut evidence of the importance of the hippocampal zone for recent memory comes from operations reported by Scoville^{12,13} which supplement our study with the exactness of a planned experiment. In a series of deteriorated schizophrenic patients, he carried out the operation which he has called "bilateral uncotomy" or "bilateral medial temporal lobectomy," depending upon the extent of the excision, and which

he did in the hope of discovering an effective surgical treatment for schizophrenia, free from the undesirable side-effects of radical frontal lobotomy.¹²

These operations were made through large bilateral trepanations, and the excisions were made by bisecting the tip of each temporal lobe and removing bilaterally the inferior portion of each temporal lobe which lay mesial to the inferior horn of the ventricle. The posterior extent of the removal varied. In most of the medial temporal lobectomies the excision was carried back a distance of 5 or 6 cm., as measured from the temporal tip. In the "uncotomies" the limit was more anterior, the removal being limited to the uncus and amygdaloid region. In none of these cases was any pronounced memory disturbance noted at the time of operation.

In two other patients, however, one an epileptic and the other a psychotic, Scoville carried the removal backward to a greater distance, hoping thereby to obtain more satisfactory therapeutic improvement. Actually, in these cases the excision extended back to a point roughly 8 cm. posterior to the tips of the temporal lobes, so that the ablation must have included the major portion, if not all, of both hippocampi and hippocampal gyri, as well as the uncus and amygdala bilaterally.

After operation these patients showed an immediate and grave loss of recent memory, although they apparently could still remember childhood scenes quite accurately. They could not remember, or relearn, the location of the bathroom, although they retained due consideration for the proprieties of ward life.¹³

Scoville has allowed one of us (B. M.) to carry out psychological studies of these patients, and we conclude that these two patients have, each of them, a memory defect exactly similar in type to that of our two cases. Furthermore, there is no evidence, in his patients, of improvement up to the present time, two and one-half and three years after operation.

These observations, together with comparative studies of other patients with less extensive removals of the mesial temporal lobe, are reported in detail elsewhere.¹⁴ They provide striking confirmation of our assumption that the defect in the postoperative memory of our patients (Cases 1 and 2) was due to bilateral absence of function in the hippocampal formation. Scoville and Milner¹⁴ find no evidence of memory deficit, even to formal testing, when the bilateral removal is limited to the uncus and amygdala.

Comment

Evidence accumulates that the temporal lobes contribute to the mechanisms of memory recording, memory recall, and comparison of present experience with the record of the past.¹⁵

Experiential Seizures.—Regional discharges produced by an epileptogenic area of cortex seem to sensitize the cortex of the temporal lobe in such a way that stimulation under local anesthesia occasionally reveals its true functional secrets. Thus, mild electrical stimulation of the lateral or, more frequently, the superior surface of either temporal lobe may cause the conscious patient to relive a sequence of experiences from his life, experiences of months or years past. It is apparent that there is an enduring record of the stream of consciousness within the brain of each man—the stream of personal experience containing those things to which he paid attention and of which he was therefore conscious in each succeeding interval of time, things both important and unimportant, experiences that had been sometimes remembered, sometimes forgotten.

Location of Experiential Record.—Evidently there is a sequence of facilitated neuron connections somewhere which, when activated, is capable of producing a "play-back," like a wire recorder or a gramophone, when stimulated. Where is that sequence located? It has seemed likely that it was not beneath the electrode on the surface of the temporal cortex, but rather in some

more distant connected ganglionic area. It was suggested hypothetically that this area was in the hippocampal zone of each temporal lobe.¹⁶ We may examine this hypothesis in the pages that follow.

The Memory Defect.—Psychological study of our cases (and of the two examples of bilateral hippocampectomy reported by Scoville) demonstrates a remarkably clear-cut symptom complex, which is exactly the same in each case. The Intelligence Quotient shows no change, and professional skills (whether for preparing blueprints or for making gloves) are well retained. Vocabulary is also intact. #

The difficulty with recent memory was a general one, affecting both verbal and non-verbal material. There was no corresponding loss of attention, concentration, or reasoning ability.

It was found that all four patients could retain in mind a sentence or a short sequence of numbers, provided they were permitted to keep their attention upon it, even as long as 15 minutes if no one spoke to them. But if they turned attention to something else, even momentarily, they might forget the previous matter completely, might even forget that there was a "previous matter."

This suggests that the recording mechanism for the stream of conscious experiences normally preserves that record in the hippocampal area, as the person turns his attention to something else. An essential part of that mechanism must have been re-

B. (Case 2), who had suffered transient post-operative aphasia, which made its appearance 24 hours after removal of the anterior portion of the left temporal lobe, at the time of the first operation, had no aphasia following the second operation, when the hippocampal formation alone was removed.

The memory defect appeared immediately after this second operation and has been relatively constant during the past three years, although there was some improvement in the first year after operation. His loss of recent memory is less severe than in the other three cases, and it is possible that the hippocampal-zone destruction on the right (nonoperative) side is only partial.

moved in the bilateral operation. It would seem that while a proposition is retained within the spotlight of attention, the central integrating mechanism can deal with it without reference to the record which is normally being made. All this would be quite consistent with the hypothesis expressed above.

Retrograde Amnesia for a Preoperative Period.—But the explanation is not quite as simple as that just suggested. These patients have also had retrograde amnesia for preoperative events, and complete loss of memory for the relatively recent past with reasonably good capacity to recollect the distant past. In Case 1, A., the preoperative forgetting, immediately after operation, went back four years, but the patient could recall some details of his childhood experience. He was unable to recognize a "girl friend" whom he had seen frequently, but only during the 18 months before operation!

In our own patients whom we could follow at frequent intervals, the preoperative amnesia has gradually come to cover a shorter space of time, and various events, formerly forgotten, have gradually emerged from the retrograde oblivion.

This evolution is characteristic also of the retrograde amnesia produced by severe cerebral concussion. It, too, spreads backward over a man's life from the time of the blow and then, as it clears up, moves forward toward the time of the accident.

A partially satisfactory explanation may be found in the following line of reasoning:

The record of the stream of consciousness, which, we believe, depends upon the integrity of the bilateral hippocampal structures, cannot be called into activity voluntarily except for a relatively short period of time. The record is, no doubt, used for the purposes of comparison during much longer periods. Later on, a person deals with what may be called generalizations, and he can summon them to his purposes. All events, even "memorable" ones, slip away from the reach of voluntary recall unless

he has talked about them or preserved them by reflective reconsideration.

For example, one remembers a song or a poem that has been heard repeatedly. One forgets each hearing or reading, but one remembers the generalization.

When the stimulating electrode causes a patient to hear a song, it is one specific hearing of it. The patient can identify the instruments in the orchestra or the voice or piano. But if he recalls the song voluntarily, he may sing it through with no remembrance of the varied experiences that went together to create his memory of it.

If the electrode causes the patient to hear the voice of a well-known friend, and perhaps to see the friend as well, it is the friend as he was seen and heard on one specific occasion only. The electrode re-activates the record of the stream of consciousness and re-presents one experience. But if the person voluntarily recalls the friend, he gets only a generalization. That is his memory of the friend, and the memory is made up of many fragments of past experience.

Words are like that. On the first day or two, when a new word is first heard, it forms a part of one or more experiences. But after the word is "learned," it loses the former context that belonged to each hearing, like the song. The word then can be voluntarily recalled through the agency of neuron mechanisms in the speech areas, doubtless those so familiar to us in the cortex of the dominant hemisphere.

These patients did not become aphasic, nor did they lose the capacity to sing songs that were previously learned. They lost only the record of the stream of consciousness. These things, which they could still remember from the past, might well be the generalizations.

B. remembered his wife and the name of his surgeon, Dr. Penfield, a name he had known for five years. But he could not recall the names of the nurses and house surgeons whom he had known only for a week or two before operation. Why, then,

should A. fail to recognize his "girl friend" of 18 months' acquaintance? Why the long period? This we cannot explain.

Automatism—Interference with Recording.—Both these patients (Cases 1 and 2) became automatic during preoperative attacks. Aside from a brief warning aura, the whole attack consisted in automatism.* During such attacks no record is made of the stream of experiences, to judge from the fact that the patient has subsequent amnesia for the whole period. This is an amnesia which never clears up.

Temporal-lobe automatism, as demonstrated by Feindel and Penfield,⁷ is produced by an epileptogenic discharge in the region of the uncus, amygdaloid nucleus, and hippocampal gyrus. It may be readily produced by electrical stimulation in the periamygdaloid area, provided the stimulation launches a local attack with electrical after-discharge. Local epileptic discharge in that area seems to fire into the central mechanism, in the brain stem, which is concerned with memory recording in the two hippocampal zones. This central interference probably accounts for the arrest of all recording.

On the other hand, epileptic discharge in, or electrical stimulation of, the cortex of the superior or lateral surface of the temporal lobe sometimes produces the opposite effect. It activates a strip of the record of past experience, and the patient has what we have called an experiential seizure. During it the patient relives some earlier period of time.

The man who has lost the bilateral hippocampal mechanism cannot form a new record of his current experience. This may

be because the place where the record is laid down has been removed, or it may be that the hippocampal zone is normally utilized to lay down the record in some other area.

The patient carries on, however, with the help of those things that have been learned, preserving the concepts that have been generalized from his daily experience. He remembers words, rules of behavior, even oft-recollected scenes from childhood, and retains his former skills. Each of our patients has continued to earn his living—the one as a glove cutter, the other as a draughtsman.

Conclusions

Bilateral removal of the hippocampus and hippocampal gyrus in man produces loss of recent memory. As soon as he has turned his attention to something else, the patient is unable to remember what was happening a moment earlier. It is as though he had made no record of present experience. He also has a retrograde memory loss that covers a considerable period before operation.

This is a confirmation of the suggestion of Glee and Griffith,⁹ based on the evidence of autopsy study of a patient with bilateral brain lesions. "The suggestion is made," they wrote, "that the hippocampal formation of the adult seems to be essential for recent memory." In their case, as well as in our cases, the hippocampal gyrus was destroyed along with the hippocampus.

Psychological study of our patients shows that, in spite of the above-noted deficiencies, memory for the distant past is not lost, nor is there corresponding loss of attention, concentration, reasoning ability, or previously acquired skills. The intelligence quotient shows no drop when compared with preoperative testing. There is no interference with speech, and the memory of words is unimpaired.

We may conclude that an essential part of the recording mechanism is contained in the hippocampal zone. Certainly, also,

*Automatism may be defined as a state of altered consciousness. The patient usually stares blankly at the outset, and this serves as a signal to those who know him that he is out of contact with them. He usually appears confused and fumbles about, making chewing and swallowing movements. Gradually he may become less obviously confused. He may speak and go about some activity of his own, often ill directed, until suddenly he is himself again and wonders what he has done, what has happened.

another part of the mechanism lies in the central integrating circuits of the brain stem, circuits that have duplicate connections with the two hippocampal areas.

These conclusions are based largely on the postoperative study of four patients in whom this distressing complication appeared. Two of our own were found to have this defect after unilateral excisions had been carried out in the treatment of temporal-lobe epilepsy, the contralateral hippocampal zone apparently having been injured by incisural herniation at birth. Two patients were added, for us to study, in whom bilateral hippocampectomy had been carried out by Dr. William Scoville,[†] in his search for a better operation to replace frontal lobotomy as a treatment for hopeless psychotics. The symptom complex was identical in all four.

This case analysis was undertaken originally because of remorse that two of our patients should have suffered a complication. It is a severe handicap to them, although both continue to earn their living, which had been threatened by the frequency of their preoperative cerebral seizures. But the study, which was intended primarily to serve as a warning so that others, as well as ourselves, might avoid this pitfall, has opened up new and exciting evidence.

Neurosurgeons who hope to cure temporal-lobe seizures by removal of one anterior temporal lobe and all of the hippocampal zone should bear in mind that the squeezing of the baby's head at the time of birth, which produces temporal herniation and incisural sclerosis,⁶ may occasionally destroy the hippocampal zone on one side and injure that zone on the other. Thus the major epileptogenic discharge may be on the side of the less severe injury. Removal of the zone on that side might then be

expected to result in this loss of recent memory. Such a loss is what occurred in the two cases that we have reported.

We have carried out careful psychological study of more than 90 other patients before and after the same unilateral operation, and they showed no evidence of general memory loss. Under normal conditions one hippocampal area duplicates the work of the other and carries on when one is removed.

For the time being, in order to guard against such memory losses, we have adopted the policy that when the initial electroencephalographic study points to independent abnormality in both inferior temporal regions, no removal should be made of either hippocampal zone.

The analysis of this complication of recent memory loss, undertaken as a neurosurgical project, has thrown welcome light on the location of some portion at least of the ganglionic record of current experience. It has demonstrated that this record is anatomically separate from the neurological mechanisms that are related to words, skills, and concepts that have been preciously acquired.

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MEMORY DEFICIT DUE TO BILATERAL HIPPOCAMPAL LESIONS

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Encephalography by the Displacement Technique

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The commonly accepted technique of performing encephalography has been to replace a volume of spinal fluid with an equal volume of air or other gases. Adaptations of this technique have been made by Gardner and Nichols,¹ by Davidoff and Dyke,² and by Lindgren,³ who used smaller quantities of gas and/or first injected air before withdrawing any spinal fluid. In 1955 Slosberg et al.⁴ introduced a new technique of encephalography, which was called the "minimal withdrawal technique." This consisted of injecting 10 to 80 cc. of air into the lumbar subarachnoid space while withdrawing no more than 5 cc. of spinal fluid. A group of 35 patients was studied. Three of these had early papilledema, and four had spinal fluid pressures above 200 mm. H₂O.⁵ An average of 44 cc. of air was injected. Five patients had no headache during the procedure, but these had an average of only 24 cc. of air added. After seven hours most patients were asymptomatic, and after 24 hours only one patient still had a severe headache. The patients in this study who had brain tumors had no more symptoms following the procedure than did those without tumors.⁵ Slosberg and associates⁴ concluded that their technique produced "a marked reduction in the duration of discomfort following pneumoencephalography."

They later reported 84 additional patients upon whom air studies were performed, 64 by the minimal withdrawal technique and 20 by the more usual technique.⁶ They again concluded that postprocedure headache, temperature elevations, vomiting, and chills were less in the minimal withdrawal group. Two deaths occurred in the group of 20 who had pneumoencephalography with the usual technique, and one death occurred in the minimal withdrawal group, of 64. This patient was operated upon the day of the procedure; a glioblastoma was found, and she died on the fourth postoperative day.⁵

The present study was undertaken to evaluate the patients' reactions, spinal fluid pressure changes, and x-ray results of the technique of encephalography, as described by Slosberg et al.⁴ This technique has been designated by us as a displacement technique, since spinal fluid is displaced rather than replaced by air.

Methods and Materials

The pneumoencephalograms of 50 consecutive patients are reported. The only element in selection was the elimination of patients in whom there was elevation of the cerebrospinal fluid pressure or of those who had definite clinical evidence of an expanding intracranial lesion. The prepneumoencephalographic clinical diagnoses in these patients

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TABLE 1.—*Prepneumoencephalographic Diagnoses*

Generalized seizure disorder, idiopathic.....	17
Generalized seizure disorder, post-traumatic.....	6
Focal seizures of unknown cause.....	7
Central nervous system syphilis.....	2
Cerebral thrombosis.....	9
Intrasellar tumor.....	2
Post-traumatic encephalopathy.....	2
Brain abscess.....	1
Cerebellar degeneration.....	1
Porencephalic cyst.....	1
Multiple sclerosis.....	1
Laurence-Moon-Biedl syndrome.....	1
	50

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are shown in Table 1. There were 38 male and 12 female patients. The average age was 48, with a range from 13 to 70 years. Patients were premedicated with 0.4 mg. of atropine sulfate I. M. and 100 mg. of pentobarbital sodium P. O. prior to the procedure. Spinal fluid pressures were recorded with the patient in the lateral decubitus and sitting positions before any air was injected. A 22-gauge spinal needle was used in an attempt to reduce the dural tear and to minimize the loss of spinal fluid if a connection should loosen during the procedure. Fifteen cubic centimeters of air was first introduced while the patient was sitting with his head extended, and a lateral film was taken to demonstrate the basal cisterns alone. Prior to the next film, the ears were taped forward so that they would not interfere with visualization of the fourth ventricle. The head was then placed in midflexion; 20 cc. of air was introduced, and another lateral film was taken. At this point, a sitting spinal fluid pressure was recorded. The patient was then put in position for a posterior-anterior upright film, which was immediately developed and inspected for evidence of a ventricular shift. If a shift was found, the procedure was continued, utilizing only the initial quantity of air introduced. If no mass was seen, additional air was added, the amount depending upon the amount of filling, usually about 30 cc. A sitting pressure was taken; the patient was placed on his side on the x-ray table; a final pressure was taken, and the needle was removed. The average duration of the procedure to this point was 30 minutes. The average amount of air injected was 67 cc., with a range from 35 to 120 cc. Conventional x-ray views were taken in the recumbent, prone, and lateral positions. Vital signs and the patients' complaints and symptoms were followed during and after the procedure until they returned to preprocedure levels. Each patient received two lumbar punctures in the postprocedure period to evaluate pressure and cell changes.

Symptoms and complaints were judged as being mild, moderate, or severe. Headache and other complaints were usually first treated with 0.6 gm. of acetylsalicylic acid P. O. every three hours, and severe discomfort was treated with caffeine and sodium benzoate U. S. P., 500 mg. I. M. every three hours. If the above medication did not control the patient's complaints, the choice of analgesic medication was at the discretion of the ward physician.

Continuous recordings of spinal fluid pressures during and after addition of the air were obtained on four patients. Three of these were made using a Satham gauge attached to the spinal needle, and pressure tracings were photographed from a multichannel oscillograph. The level of reference was the level of the needle. A continuous spinal

fluid pressure recording was made on a fourth patient using a 90 cm. manometer with a 1 mm. bore. Details of the techniques are described under "Results."

The x-rays were evaluated, emphasizing gas volume and gas distribution. Anatomical visualization of subarachnoid spaces, cisterns, and ventricles were described. Special note was made of the basal cistern and fourth ventricle views.

Results

For evaluation of symptoms and signs, 48 of 50 patients were used. Two were eliminated in the evaluation because cerebrospinal fluid was removed in an attempt to fill the ventricular system. These two patients therefore did not fulfill the criteria for the displacement technique. The symptomatology reported, therefore, is that of patients who had approximately only 1 cc. of spinal fluid removed. Symptoms which occurred during the procedure are listed in Table 2. All of the patients had headache during the procedure. In 26 (55%) it was severe, and in 22 (45%) it was mild or moderate. Severe headache occurred in patients who had larger quantities of air injected, and the headaches usually increased in intensity in proportion to the amount of air injected. Nausea occurred in 21 (44%) and vomiting in 11 (23%) during the procedure. Mild perspiration occurred in six patients (13%) and pallor in two patients (4%). Vital signs did not change significantly during the procedure; nor did any of the patients show evidence of shock, as manifested by alterations in pulse and blood

TABLE 2.—Symptoms During the Procedure

Type Symptoms	% Patients with Symptoms
Mild headache.....	4
Moderate headache.....	41
Severe headache.....	55
Vomiting.....	23
Perspiration.....	13
Cyanosis.....	0
Pulse change.....	0
Nausea.....	44
Pallor.....	4
Backache.....	6
Stiff neck.....	2
Dizziness.....	2
Chills.....	4
Yawning.....	10
Belching.....	2
Seizures.....	4

TABLE 3.—Percentage of Patients Showing Postprocedure Symptoms

Hours from Procedure	No Reaction	Mild Head-ache	Moderate Head-ache	Severe Head-ache	Vomiting	Chills; Perspiration	Cyanosis	Pulse Change	Nausea	Restlessness; Crying	Pallor	Back-ache	Incontinence	Stiff Neck	Drowsiness	Dizziness	Mental Changes
The Displacement Technique (46 Patients)																	
1-6	9	21	33	18	13	6	0	0	15	0	0	0	0	2	3	2	3
7-12	21	15	28	7	2	0	0	0	8	0	0	0	0	6	2	0	0
13-24	29	31	19	0	9	0	0	0	15	0	0	0	0	17	2	2	0
25-48	56	31	16	0	2	0	0	0	11	0	0	0	0	13	2	0	0
49-72	67	26	4	0	2	0	0	0	5	0	0	0	0	13	0	0	0
73-96	83	15	2	0	2	0	0	0	2	0	0	0	0	0	0	0	0
97-120	85	8	2	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Bohn's Statistics (1000 Patients)																	
0-12	8	4	55	3	36	22	17	9	8	8	7	3	3	2	2	1	1
13-24	23	7	49	3	12	1	0	1	3	9	1	3	5	1	1	0	1
25-48	21	15	45	2	8	1	0	1	4	8	0	3	6	2	2	2	1
49-72	43	11	27	1	5	0	0	0	3	6	0	1	4	1	1	2	1
73-96	55	9	17	1	4	0	0	0	2	4	0	0	3	1	1	1	1
97-120	56	7	12	1	3	0	0	0	2	2	0	0	3	1	1	1	1

pressure, profuse perspiration, faintness, and severe pallor.

Following the procedure, no severe headache was reported after 12 hours, and most moderate headache had disappeared at the end of the second day. Twenty-seven (56%) of the patients were totally asymptomatic by the end of the second day, and 41 (85%) were totally asymptomatic by the end of the fifth day.

These results differ from those of Bohn,⁷ who reported 1000 patients who had encephalography by the usual replacement technique. Twenty-one per cent of his patients were totally asymptomatic by the second day, and 56% were totally asymptomatic by the fifth day. A comparison of the results of this present study and that of Bohn⁷ is shown in Table 3, but it is clear that these two series cannot be accurately compared, because of the lack of controls.

After the procedure, the only significant change in vital signs was an elevation of the rectal temperature, which tended to occur at two different times. One elevation, averaging 100.9 F, occurred at 7-12 hours, and the other, averaging 100.3 F, occurred at 25-36 hours. The second elevation was associated with an increase in nausea, vomiting, and stiffness of the neck, which occurred from 13 through 48 hours (Table 3). The spinal fluid cell counts were also highest from 7 through 48 hours (Table 4). It appears that this secondary increase in temperature, symptoms, and spinal fluid cell count was caused by a meningeal reaction to air.

The amount of postprocedure analgesic medication administered is summarized in Table 5. Several patients required no medication. The average medication required per patient was 4 acetylsalicylic acid tablets (1.2 gm.) and 1.3 injections of caffeine and sodium benzoate U. S. P. (670 mg.).

In 24 patients, measurement of spinal fluid pressure with the patient on his side revealed it to be the same prior to and after the procedure (Table 4). Pressure measurements on 15 patients midway during the

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TABLE 4.—Vital Sign and Spinal Fluid Changes

	Average Rectal Temp., Degrees F	Average Pulse	Average Blood Pressure	Average Respirations	Spinal Fluid Pressure *	Spinal Fluid Protein †	Spinal Fluid Cells	
							Average Lymphs.	Average Polys.
Control	98.8	79	125/75	18	137	36	2	0
Mean maximum change during procedure	--	85	130/80	20	161			
Immediately postprocedure	99.7	82	128/81	20	149	43	26	4
1-6 hr.	100.9	82	125/76	20	150	68	364	0
7-12 hr.	99.8	79	126/76	20	138	27	35	4
13-18 hr.	99.7	84	122/80	20	170	27	415	2
19-24 hr.	100.3	83	124/76	20	123	48	134	34
25-36 hr.	99.3	82	119/73	20	122	55	129	54
37-48 hr.	99.4	81	122/75	20	132	44	90	18
Third day	98.9	83	125/76	20	149	37	37	2
Fourth day	99.0	85	130/70	20	164	27	24	1
Fifth day	99.2	86	125/74	20	116	45	48	0
Sixth day								

* Patient on his side.

† One elevated protein pre- and postprocedure not included.

procedure, after 35 cc. of air had been injected, revealed that the pressures rose and then began to fall. This led to the

continuous recording of spinal fluid pressure changes in four patients.

Two patients had the total quantity of air added over a short period of time, and recordings were immediately begun. In one patient 50 cc. of air was injected over a five-minute period with the patient sitting. He was then placed on his side and recording was begun. This record is shown in Figure 1A. It can be seen that the resting pressure was 105 mm. H₂O, the postinjection pressure was 205 mm. H₂O, and the pressure fell almost to control levels in 10 minutes. The second patient had a total of 60 cc. of air added over 2 minutes 48

TABLE 5.—Postprocedure Analgesic Medication

Type and Number of Doses of Analgesics				
Acetyl-salicylic Acid, 0.6 Gm.	Caffeine Sodium Benzoate, 500 Mg. I. M.	Codeine Sulfate, 30 Mg. P. O.	Meperidine, 75-100 Mg. I. M.	
Time from end of procedure				
1-6 hr.	17	28	0	1
7-12 hr.	7	7	2	0
13-24 hr.	9	9	1	2
25-48 hr.	24	9	1	0
Third day	18	5	3	0
Fourth day	10	5	1	0
Fifth day	9	1	1	0
Sixth day	4	0	0	0

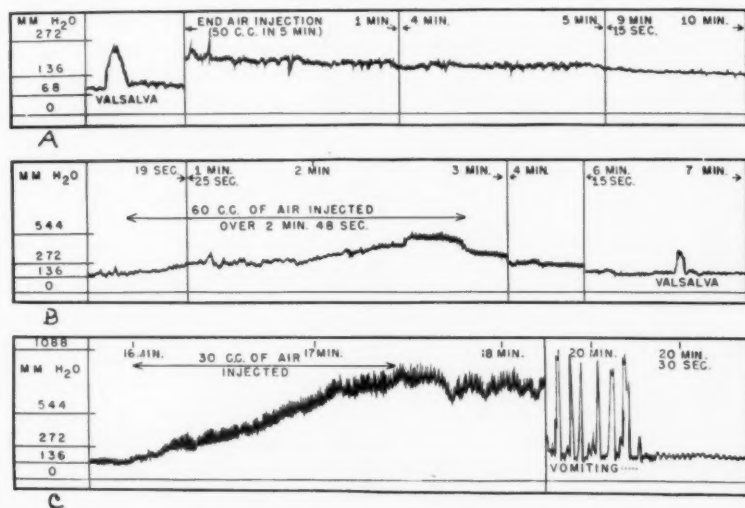


Fig. 1.—Changes in spinal fluid pressures.

seconds while he was in the sitting position. Two needles were placed in two separate interspaces in the lower lumbar area. While air was injected through the upper needle, pressure recording was made through the lower one. Figure 1B shows that the initial pressure was 136 mm. H_2O , the pressure was 544 mm. near the end of the injection, and the pressure had begun to fall before the injection was finished. By 2 minutes 12 seconds after the end of the injection, the pressure was again at control level.

Two patients had increments of air added while they were in the sitting position, and the time intervals between injections, and the head positions during the injections, duplicated the conditions which usually occurred during the air study. Again, two needles were inserted, one for the addition of air and one for recording pressure. Figure 1C shows the pressure changes after the third addition of 30 cc. of air. (Not shown are the first two and the last increment, which elevated the pressure to 600-800 mm. H_2O . After these additions the pressure fell to control levels in two minutes.) The recording in Figure 1C shows that the third increment elevated the spinal fluid pressure to 1025 mm. H_2O , and it fell to control levels in 2 minutes 15 seconds. The large spikes

are due to elevation of spinal fluid pressure during vomiting.

Figure 2 demonstrates pressure changes when four increments of air were injected in another patient in the upright position, utilizing the manometer to measure pressures. After each injection the pressures returned to or below control levels in from three to four minutes. At the end of the study, after 80 cc. of air had been injected, the sitting pressure was 300 mm. H_2O , as compared with a control pressure of 420 mm. H_2O .

Visualization of cerebral structures was considered adequate in 47 of 48 studies in which the displacement technique was solely used. Pneumoencephalographic diagnoses were as follows: normal study, 15 cases; focal or generalized ventricular dilatation and/or cortical atrophy, 28 cases; right posterior temporal mass, 1 case; intra- and suprasellar masses, 2 cases, and cavum septum pellucidum, 1 case.

The special position for demonstrating the basal cisterns was attempted in 37 patients (74% of studies) but added information in only 2 patients. In 49 patients the brow-up lateral position demonstrated the basal cisterns most clearly and adequately. The fourth-ventricle view was attempted in

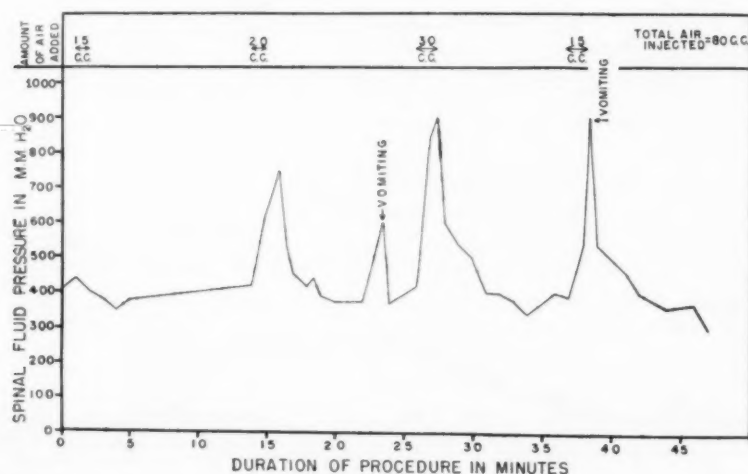


Fig. 2.—Lumbar manometric measurements during air injections (patient seated).

41 patients and was successful in 22 patients.

Follow-up films to evaluate absorption of air were made in nine patients. A brow-up lateral film was used to visualize the amount of remaining air. Surface air usually disappeared in the first 24 hours. In three patients with normal studies air had been absorbed between three and six days. In the others, who had ventricular dilatation, absorption occurred between 6 and 15 days.

Recapitulation of Steps in the Procedure

From the above experiences, the technique of encephalography by the displacement technique has the following sequence: First, the procedure is explained to the patient, and the head positions he is to take are demonstrated to him. The entire procedure is performed in the x-ray room. The patient is seated on a revolving chair or stool, and a lumbar puncture is performed with a 22-gauge needle. A three-way stop-cock with a length of rubber tubing is attached to the needle. The patient is positioned with the back erect and the chin in the midflexion attitude. The ears are taped forward. Twenty cc. of air is injected, and a lateral film is taken during the injection of the last 5 cc. of the amount to demonstrate the fourth ventricle, aqueduct, and posterior portions of the third ventricle. If the fourth ventricle or posterior fossa is of particular interest, a posterior-anterior view is taken with the chin in the midflexion position. The head is then slightly elevated so that the chin and nose are touching the cassette. This position is used in preference to the nose-forehead position so that air will be distributed in the anterior as well as the posterior parts of the lateral ventricles. A posterior-anterior upright film is taken, and this is called the "scout" film. It and the fourth-ventricle view are then developed and inspected for evidence of ventricular shift. If there is a shift, the procedure should continue with conventional views, utilizing the air already present. If there is no shift, and depending upon the amount of filling

and the size of the ventricles, more air (usually 20-40 cc.) is added. This air is added with the head in the midflexion position with the patient sitting. The needle is withdrawn, and again posterior-anterior and lateral upright views are taken. The patient is placed on the x-ray table, and conventional views are taken. If by chance all the air had entered the ventricles, a second spinal tap may be performed and 15 cc. of air added with the head extended. This usually places an adequate amount of air over the surface and in the basal cisterns. If the basal cisterns are of particular interest, the study may begin with this maneuver; however, air over the surface frequently obscures the fourth- and third-ventricle shadows.

Comment

It was observed during the procedure of adding air to the subarachnoid space without the withdrawal of cerebrospinal fluid that the cerebrospinal fluid pressure did rise; in one patient it rose as high as 1025 mm. of cerebrospinal fluid. The prompt return of the cerebrospinal fluid pressure to normal levels in from 2 to 10 minutes after the addition of the air indicates a spinal-fluid-pressure homeostasis. Pressures taken at the beginning and at the end of the procedure were essentially the same. The nervous system actually accommodates a larger volume than the volume of air injected, due to expansion of air, as it is warmed by body heat, the vapor pressure of spinal fluid, and the negative pressure which exists in the ventricles.

The mechanism of this pressure adjustment is not entirely clear. The speed with which adjustment occurs suggests that a vascular mechanism may be functioning, either by a collapse of venous channels or by an active constriction of arteries, due to irritation by the air. The subarachnoid space is not a rigid area, and it will accommodate varying quantities of fluid. It is possible that some fluid is displaced into the spinal subarachnoid spaces, where it distends the root sleeves and caudal sac. Spinal fluid

absorption or leaks at the needle site perhaps occur, but the change seems too rapid to accept this explanation. Rapid absorption of the air may play a part; but this does not appear to be an adequate explanation, for a similar rise and rapid fall occur if isotonic saline is used to elevate the spinal fluid pressure.⁸

Increases in intracranial pressure present over a short period of time appear to be of no harm to patients. Pressure elevations of 800 to 1000 mm. H₂O may occur for hours during general anesthesia.⁹ Wolff¹⁰ reported four cases in which sitting lumbar pressures were elevated to 680-850 mm. H₂O with intrathecal saline. No ill effects were seen. Foldes and Arrowood⁸ also raised the spinal fluid pressures from 200 to 570 mm. H₂O by intrathecal saline with the patients supine. When the infusion was discontinued, the pressures fell to near-normal in four or five minutes. These results are similar to the ones reported here.

It is not known whether this adjustive mechanism continues to function when the normal fluid circulation is interfered with, when the intracranial space is partly filled with a mass, or when the normal spinal fluid pressure is elevated. Until the above questions are clarified, this procedure should be applied with caution to patients with intracranial masses and increased intracranial pressure.

Headache, nausea, and vomiting occurred commonly during the procedure, but it was most impressive that no patient showed symptoms of shock. Headaches decreased in intensity rapidly, and no severe headaches were reported after 12 hours. The mildness of the reaction to the procedure is reflected in the small amount of medication that was necessary to control postpneumoencephalography symptoms. Over half of the patients in this study had dilated ventricles and/or cortical atrophy. This type of patient has been noted by others to show a less severe reaction to air studies. In the present study this was also noted, but the group without cortical atrophy and the patients with

masses also showed mild, short-lived symptoms.

Summary and Conclusions

Pneumoencephalograms were performed upon 50 patients. The technique consisted of the injection of an average of 67 cc. of air with the withdrawal of no spinal fluid, except for 1 cc. for protein and cell determinations.

The displacement technique of encephalography appears preferable to those techniques whereby spinal fluid is removed, as the symptoms during and after the procedure are reduced and the x-ray results are equally as good as those obtained by the replacement method.

(a) These patients usually showed headache, nausea, and vomiting during the procedure, but their vital signs were stable and none showed shock.

(b) The maximal rectal temperature elevation was 100.9 F between 7 and 12 hours. There was a secondary rise to 100.3 F between 25 and 36 hours, which seemed to parallel the development of signs of meningeal irritation.

(c) Twenty-seven patients (56%) were totally asymptomatic by the end of the second day, and forty-one (85%) were totally asymptomatic by the end of the fifth day.

(d) Postprocedure medication averaged 1.2 gm. of acetylsalicylic acid and 670 mg. of caffeine and sodium benzoate U. S. P.

In 47 patients cerebral structures were well visualized by x-ray.

Spinal fluid pressures which were taken before and after the procedure showed no change.

Four continuous spinal fluid pressure tracings were recorded during and after the injection of from 50 to 80 cc. of air into the lumbar subarachnoid space. The spinal fluid pressures did rise, but fell to normal in from 2 to 10 minutes.

Dr. Andre Cournand and his co-workers made the facilities of their laboratories available for the performance of the spinal fluid pressure studies. Dr. Paul Slosberg provided data as yet unpublished and made helpful suggestions.

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Loss of Consciousness and Convulsions with Congenital Heart Disease

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Introduction

The history of a paroxysmal loss of consciousness or convulsions occurs in approximately 18% of cases of congenital heart disease.¹ Knowledge of the factors producing these disturbances is based on clinical observations of a few physicians who have had wide experience in dealing with congenital heart disease. White (1937)² stated: "The greater the degree of cyanosis, the greater the likelihood of seizures." Abbott³ noted: "Epileptiform

seizures occur in severe cases and seem to be related to the anoxemia present rather than the raised oxygen unsaturation." It seemed worthwhile to discuss in detail, with some documentation, the factual basis for these statements derived from a large number of patients seen with congenital heart disease.

Material and Methods

We have analyzed the records of 336 patients with congenital heart disease who gave the history of either loss of consciousness or a convulsion; all were patients at the cardiac clinic of the Harriet Lane Home, of The Johns Hopkins Hospital.

Incidence

In this series, 227 patients had at least one episode of unconsciousness (exclusive of convulsions), and 109 patients had at

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TABLE 1.—*Distribution of Convulsions and Convulsive Disorders in Congenital Heart Disease*

Form of Congenital Heart	Total No. of Cases	No. Cases with Loss of Consciousness	Percentage (Exclusive of Convulsions)	No. Cases with Convulsions	Percentage (When Significant)
Tetralogy of Fallot	1045	176	17.4	71	6.8
Tricuspid atresia and stenosis	18	2	--	2	--
Single ventricle	10	2	--	0	--
Transposition with pulmonary stenosis	16	1	--	1	--
Single ventricle with pulmonary stenosis	10	3	--	0	--
Truncus arteriosus with decreased flow	94	13	13.9	6	6.1
Transposition	109	13	11.9	8	7.4
Transposition with tricuspid atresia	4	0	--	1	--
Ebstein's malformation	19	0	--	1	--
Pure pulmonary stenosis	110	1	0.9	3	2.7
Truncus arteriosus with normal flow	10	0	--	0	--
Eisenmenger's syndrome	123	12	12	6	4.9
Truncus arteriosus with increased flow	10	0	0	0	--
Interventricular & interauricular septal defects	138	0	0	5	3.6
Patent ductus arteriosus	150	0	0	5	3.1

CONGENITAL HEART DISEASE—LOSS OF CONSCIOUSNESS

least one convulsion. The incidence varied in the different forms of congenital heart disease. Table 1 is adapted from an earlier paper¹ and shows the distribution of these cases.

In general, it appears that those forms of congenital heart disease which have the highest incidence of loss of consciousness or convulsions are also those marked by the lowest systemic arterial oxygen content and oxyhemoglobin saturation.

Precipitating Factors

Loss of consciousness usually followed a severe cyanotic and dyspneic spell. A small minority of patients "fainted" at frequent intervals without preceding signs or symptoms. Three patients with transposition had sudden and unexplained periods of unconsciousness, which lasted from 30 minutes to 2 hours. Four patients with Eisenmenger's syndrome gave the history of losing consciousness after unusual exertion. One patient with pure pulmonary stenosis and a Wolff-Parkinson-White syndrome had loss of consciousness during attacks of tachycardia.

Likewise, convulsions most commonly followed severe cyanotic and dyspneic attacks. Seizures were present in two-thirds of the patients with cerebral abscess. They usually were focal, and patients had, or shortly developed, other signs of cerebral involvement. Cerebral abscess should be strongly suspected in any patient with congenital heart disease and focal seizures. The seizures related to cerebral thrombosis, in contrast, tended to be unilateral rather than focal at their onset. Five patients, all under 2 years of age, had unilateral seizures immediately prior to their hemiplegias. Seven patients had seizures following their hemiplegias.

The probable etiology of the convulsive disorder seen in 109 patients is given in Table 2.

There were, therefore, 260 patients who had disturbances of consciousness (with or without convulsions) secondary to cyanotic

TABLE 2.—*Etiology of Convulsions in Patients with Congenital Heart Disease*

Apparent Etiology	No. of Patients
Cyanotic and dyspneic attacks	55
Cerebral abscess	17
Related to cerebral thrombosis	12
Tachycardia	1
Subarachnoid hemorrhage secondary to subacute bacterial endocarditis	1
"Idiopathic"	10
Febrile illness in childhood	7
Petit mal	4
(Focal convulsions) of unknown etiology	2
Total	109

and dyspneic attacks. Since this entity is almost wholly restricted to congenital heart disease, we have tried to clarify further the role of these cyanotic and dyspneic attacks in the production of central nervous system symptoms.

In general, cyanotic and dyspneic attacks can occur in any form of congenital heart disease in which a rapid increase in the amount of venous blood delivered to the systemic circulation is possible. These attacks are most commonly seen in patients with tetralogy of Fallot. To decrease the number of variables, we have chosen to study such spells in these patients, although we believe the conclusions reached are applicable to all other types of congenital heart disease in which paroxysmal spells of cyanosis and dyspnea occur.

A general description of the spells is appropriate. Taussig⁴ describes them as follows:

Attacks of paroxysmal dyspnea are relatively common in infants and young children who suffer from severe anoxemia. At the onset of the attack some of the children will cry out and then become deeply cyanotic and gasp for breath. Sometimes an attack is precipitated by feeding, by a bowel movement or some undue exertion; at other times it occurs without any apparent cause. These attacks are sometimes so severe that the infant loses consciousness.

The severest spells may terminate with a convulsion. The spells may gradually increase in severity, or the child may have a convulsion with his first. The time of major stress is in the second year of life. The situation rarely remains constant; the spells get either better or worse. They may occur only once in a child's life, or as often as 10 to 15 times a day.

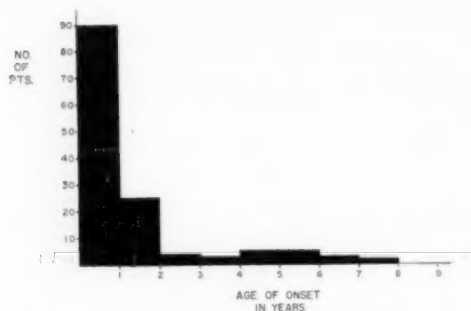


Fig. 1.—Graph showing age at which anoxic attacks began in a series of patients with congenital heart disease.

Figure 1 shows the age of onset of these spells. This corresponds to the age of development of the relative anemias of infancy, as well as the time of spontaneous closure of the ductus arteriosus in these patients.

It is apparent that almost all cases present before the age of 2 years but are rarely seen as late as the age of 7 or 8 years. In untreated cases, the natural history, if the patients survive this critical period, is represented by Figure 2, showing the age when the spells cease.

The spontaneous cessation may be related to the development of anastomotic channels of pulmonary blood flow through the bronchial circulation, or a change to solid diet higher in iron and lower in milk.

Relation to Oxygenation

It is impossible to give accurate mortality figures for the "spells," as all of the severer cases are now subject to cardiac operation of one type or another. A number of these patients had direct determinations, usually single, of the oxygen content and oxyhemoglobin saturation of femoral arterial blood. These were performed with the patient at rest. The result should be considered as the level of oxygen content or oxyhemoglobin saturation which was obtained when a standard procedure (direct blood analysis from puncture of femoral artery) was performed. In most cases it was lower than the resting level as measured by an ear lobe

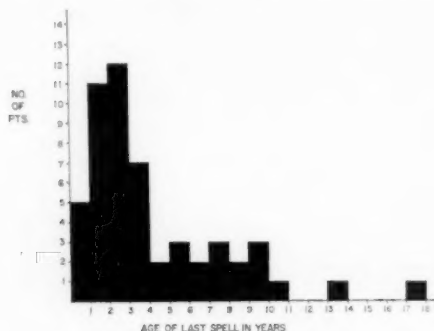


Fig. 2.—Graph showing age at which anoxic attacks spontaneously ceased in a series of patients with congenital heart disease.

oximeter* because the procedure was frequently painful and young children often cried. It does represent a value which a given patient could fall to, and as such gives a measure of the low value of the range found in patients. Often the patients with the lowest indices of oxygenation showed symptoms at the time of measurement, and this was especially true if the values remained low for any length of time. Figure 3 attempts to relate the results of these determinations to the clinical condition of the patient at the time in his life when the determination was done. The patients are classified as those having attacks terminating in convulsions, and those having loss of consciousness, during the period of hospitalization in which these tests were performed.

It is immediately apparent that all patients the oxygen content of whose femoral arterial blood count fall to less than 2 vol.% had convulsions, and nearly all of the patients with convulsions had a fall to less than 6 vol.% in a femoral arterial blood sample. It is also apparent that of those patients whose oxygen content could fall to between 4 and 10 vol.%, about one-half suffered from episodic loss of consciousness, and of those whose level fell to below 4 vol.%, 100% did.

Figure 4 is a similar plot using arterial oxyhemoglobin saturation instead of oxygen

* All values reported in this paper are based on direct blood analysis.

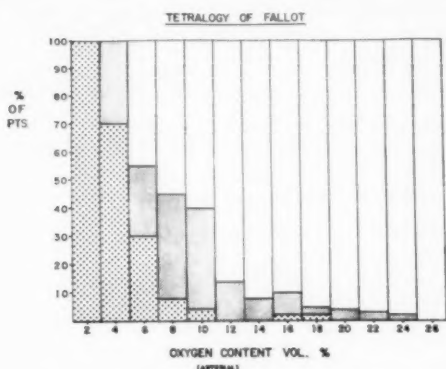


Fig. 3.—Oxygen contents of arterial blood plotted for 1000 patients with tetralogy of Fallot. Those who had similar oxygen contents were grouped according to whether or not they were having episodic convulsions (stippled columns), episodic loss of consciousness (cross-hatched columns), or no disturbance in consciousness (white column). The stippled columns, therefore, represent the percentage of patients at a given oxygen content who are subject to convulsions; the cross-hatched area represents the percentage subject to episodic loss of consciousness, and the white one, the symptom-free patients.

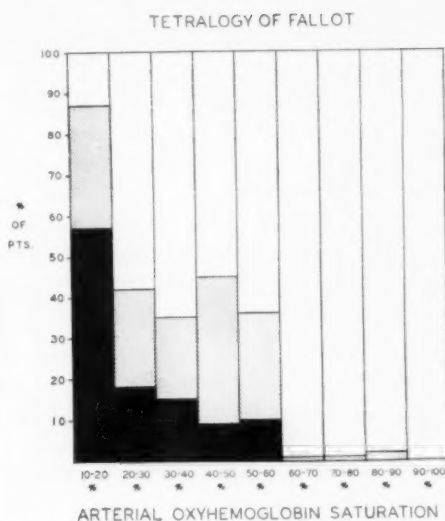


Fig. 4.—Oxyhemoglobin saturations plotted for same patients as in Figure 3. The stippled area represents percentage of patients subject to convulsions at each range of saturation. The cross-hatched area represents patients subject to episodic loss of consciousness, and the white area, the symptom-free patients.

content. These values were obtained by direct blood analysis from the femoral artery. There would appear to be a fairly critical level, at about 60% oxyhemoglobin saturation, below which disturbances of cerebral function were seen with increasing frequency. The correlation between oxygenation and loss of consciousness and convulsions can be seen when either the oxygen content or the arterial oxyhemoglobin saturation is used as an index of oxygenation. The relationship between convulsions and anoxia is demonstrated more clearly when oxygen content is used as the index of oxygenation.

The critical thresholds of oxygenation noted in the data presented are in general agreement with other work that has been done on the role of oxygen and the central nervous system in man. Schmidt⁵ has pointed out that there is no apparent change in cerebral respiration with breathing of a gas mixture containing as little as 10% oxygen in normal man, but that changes begin to appear at this level. A normal volunteer subjected to a progressive anox-

emia withstood oxygen deficiency without alarming symptoms until a percentage of a little more than 6 was reached.⁶ Armstrong⁷ noted that at altitudes of 25,000 ft. (oxygen pressure 59 mm., corresponding to inhalation of about 8% oxygen at sea level) unconsciousness usually ensued.[†]

[†] The level of oxyhemoglobin saturation obtained in the blood under these circumstances will depend upon multiple factors, including the degree of alveolar hyperventilation, the respiratory quotient, the alveolar and arterial carbon dioxide tension, and the effect of consequent alteration in blood pH on the oxyhemoglobin saturation curve. It can be estimated that the arterial oxyhemoglobin saturation varied approximately between 49% and 62% in those experiments producing mental symptoms. The oxygen content of the blood at these saturations depends on the hemoglobin content of the blood and can be calculated on the basis of the well-established fact that each gram of hemoglobin is capable of combining with 1.34 ml. of oxygen. If the subjects had a blood hemoglobin concentration of 15 gm/100 ml., the oxygen content at saturations of 49%-62% would be 9.9-11.8 vol.%. In anemic subjects, of course, the contents would be lower, and in polycythemic subjects they would be higher.

The individual differences in susceptibility to convulsions or unconsciousness in our patients may well be a function of such variables as carbon dioxide levels, changing cerebral blood flow, and arterial unsaturation. However, it is impressive that the symptoms of hypoxia produced by oxygen deprivation in normal subjects are similar to those seen in patients with congenital heart disease. Changes in consciousness appear at about the same levels of hypoxia in both.

Summary

A review is presented of the various causes of loss of consciousness and convulsions in patients with congenital heart disease.

Loss of consciousness and convulsions following paroxysmal cyanotic and dyspneic spells in patients with congenital heart disease are discussed in detail, and their relationship to hypoxia is shown.

All patients with less than 2 vol.% of oxygen in femoral arterial blood have had convulsions. All patients with less than 4 vol.% oxygen in femoral blood have had disturbances in consciousness or convulsions. One-half of the patients with 4 to 10 vol.%

of oxygen in femoral arterial blood have had disordered states of consciousness.

Disturbances of consciousness are unusual in patients with an arterial oxyhemoglobin saturation greater than 60%.

Dr. Helen Taussig and the Cardiac Clinic of the Harriet Lane Home made possible access to these patients and their records.

Peter Bent Brigham Hospital (Dr. Tyler).

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Effect of Hypothalamic Lesions on the Amygdala Syndrome in the Cat

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Introduction

Previous studies have shown that bilateral ablation of the amygdaloid nuclei and surrounding rhinencephalic structures in rodents, carnivores, and primates is uniquely characterized by a specific pattern of behavior. Animals sustaining such lesions exhibit behavior that is dominated by increased responsiveness to visual stimuli, hyperactivity, exaggerated oral activity, inability to recognize objects visually, loss of fear, and an increase in amount and diversity of sexual behavior.^{6,14-16,18-21,24}

Anatomical and electrophysiological studies of the amygdaloid nucleus and related structures have revealed efferent projections from the amygdala to widespread areas of the cortex and subcortex.^{1,8-11} More specifically, the ventromedial nucleus of the hypothalamus appears to be a strong recipient of fibers arising from the amygdaloid complex.

Electrolytic lesions of the ventromedial nucleus in cats and rats^{2,12,23} have given rise to changes in behavior characterized by savage and aggressive attacks on other animals when approached, obesity, and hyposexual activity.

In a previous publication²⁰ it was shown that the syndrome consequent to amygdaloidectomy was abolished in a cat and converted to one of savageness by a subsequently placed hypothalamic lesion largely limited to the ventromedial nucleus.

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The present experiment represents an attempt to elucidate further the functional relationship between the amygdaloid complex and certain hypothalamic nuclei through the use of serial ablations of these structures.

Method

Five male and three female cats were divided into two groups of four each for the purposes of this study. After observing their behavior in the laboratory, the cats in Group 1 sustained bilateral electrolytic lesions of the hypothalamus, three in the region of the ventromedial nuclei. Of the cats in Group 2, three underwent bilateral lesions of the amygdaloid nuclei and overlying pyriform cortex, and one sustained a unilateral ablation. After a six-week observation period, bilateral ablations of the amygdaloid complex were carried out on the animals that previously had hypothalamic lesions, and bilateral hypothalamic lesions were made on the animals that previously sustained the amygdaloid lesions. Subsequent observations were made until the animals were killed, six weeks after the placement of the second lesion.

During the course of the observation periods, the cats were housed in steel-wire cages in a temperature-regulated room and were fed a daily diet of milk and raw horse meat.

Both before and after the placement of each lesion daily observations were made of motor activity, vocalization, response to food, and affective behavior. Special attention was paid to their reaction to the approach of the observer; response to opening the cage door, handling, stroking and petting, and light tail pinch, and their reactivity to visual stimuli and other animals.

All surgical procedures were carried out aseptically under pentobarbital (Nembutal) anesthesia, and all lesions were made bilaterally in one stage. The hypothalamic lesions were placed with the aid of the stereotaxic instrument, while the bilateral ablations of the amygdaloid complex were accomplished by aspiration after mobilization of large temporoparietal bone flaps. The surgical approach and technique have been described previously.²⁰ Immediately after surgery each animal was

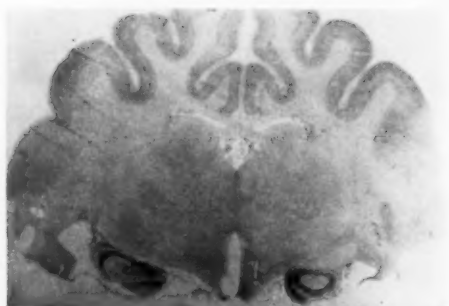


Fig. 1.—Bilateral lesions of amygdaloid and ventromedial nuclei.

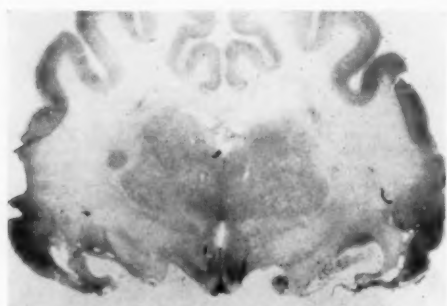


Fig. 2.—Bilateral lesions of amygdaloid nuclei and mammillary bodies.

given parenterally 100 cc. of Ringer's solution with 5% dextrose, and 300,000 units of penicillin intramuscularly. Until the animals ate spontaneously, they were given milk by gavage and spoon-fed with meat.

At the conclusion of the experiment serial sections were made of each brain; every 10th section was stained in five brains for cells and fibers by Klüver's method and three with the Nissl technique.

Results

GROUP 1.—Hypothalamic lesions followed by amygdala lesions.

1. *Preoperative Behavior.*—These observations were carried out over a two-week period; the four cats selected were very friendly and would spontaneously engage in play with the observers. They were active in their cages, walked about, rubbed head and body against the cage, and purred. When approached, they would come forward, rub against the hand, purr, and playfully paw. They could be picked up with no attempt to escape and purred all the while. They would jump out of their cages voluntarily when the door was opened, and once on the floor they would roll over on their backs and lick the observer's hand while being stroked on the belly. Allowed unrestricted movement on the floor, they wandered about, frequently coming up to the experimenter to rub against him.

Pinching their tails elicited escape activity and meowing, but with more intense stimulation they would attack. On discontinuance of the pinching, the cats could be easily handled, and they quickly regained the

friendly attitude. Their feeding behavior was not unusual. They consumed variable amounts of milk and meat but seldom finished the entire daily ration.

After a two-week observation period each of the cats in this group sustained bilateral stereotaxic lesions of the hypothalamus. Recovery from the anesthesia was uneventful, as each animal sat up and walked about with no apparent discomfort on the morning following the operation.

2. *Behavior Following Hypothalamic Lesions.*—On the first postoperative day these cats were quiet and easily managed, and by the second postoperative day they were all eating spontaneously. By the third day they began showing patterns of behavior that continued unabated until the placement of the second lesion.

With the exception of one cat, whose lesion was in the paraventricular nucleus and whose behavior was less extreme in all phases than the rest of the group, the following changes were strikingly similar for all four animals; thus they will be discussed as a group. They were inactive, remained crouched in the rear of the cage, and seldom moved about, coming forward to eat only when food was put in the cage, and even this could be discouraged by the close approach of the experimenter. When the door was opened and a hand extended toward them, they would assume a cowering position in a corner of the cage and show signs of sympathetic activity, as seen by piloerection, retraction of ears, pupillary dilation, and

growling. A slight tap on the nose would give rise to a well-directed attack with extended claws. They would frequently strike without any tactile stimulation, the only stimulus being an extended hand. The cowering and sympathetic activity exhibited by these cats occurred invariably at the mere presence of the observer.

When their cage door was opened, they made no attempt to come forward or jump out, but remained crouched in the rear of the cage. If approached slowly, they could be picked up by the scruff of the neck without signs of aggression. Held in such a position, they remained quiet and immobile until released, whereupon they immediately ran into a corner of the room and assumed a crouched position.

Stroking and petting failed to elicit any signs of purring. If they were approached, they froze into a tense position; and if tactile stimulation was attempted, they would strike out and try to escape. Lightly pinching the tail or ear of these animals resulted in marked outbursts of hissing, spitting, and high-pitched wailing, along with a savage attack with teeth and claws, which was well directed against the offending stimulus. There was considerable retention of hostility after the cessation of the stimulus, the animal being unapproachable for as long as an hour afterward.

In the presence of a dog they would retreat to a corner and cower. If the dog approached, they would attack with full fury. Mice were pounced on directly with no hesitation.

From the second postoperative day these cats ate all their customary daily ration of milk and horse meat (no additional food was given), whereas before the hypothalamic lesions they would eat only part of it. These animals gained an average of 511 gm. over the six-week period following the placement of the hypothalamic lesions.

3. *Behavior Following Bilateral Ablation of the Amygdala.*—The behavior during the first postoperative week showed transient changes from the previous behavior. The

cats were more alert; they walked about spontaneously by the second postoperative day and ate voluntarily by the third day. They would come to the front of the cage when approached, and upon opening of the door they would sit at the front for a while before jumping to the floor, where they would walk about, slowly examining objects in the room. Also in this early period they could be easily handled and petted. However, this activity was transient, and from the second week their behavior changed to the patterns described below, being strikingly similar to that seen following the first lesion.

They became inactive and unresponsive to their surroundings, and when approached would retreat to the rear of the cage, crouch, retract the ears, and exhibit pupillary dilation and piloerection. Two of the cats would strike out at the experimenter when he came close, could not be touched without gloves, and appeared even more aggressive than before placement of the amygdala lesions. The other two cats were not quite as aggressive but would strike out and hiss when touched.

They would not come out of their cages voluntarily and when placed forcibly on the floor, would go at once to a corner or to some inaccessible place in the room. There was no spontaneous vocalization, but hissing occurred at the approach of the experimenter. When lightly stroked, they remained immobile, but if the stroking continued they would turn and attack. A light pinch on the tail evoked a violent and savage response, accompanied by hissing and high-pitched screeching. Dogs and mice were reacted to in a manner similar to that after the first lesion. They would hide in the presence of a dog, but if approached they would attack him.

GROUP 2.—Amygdala lesions followed by hypothalamic lesions.

1. *Preoperative Behavior.*—In contrast to the preoperative behavior of Group 1, these four cats were shy and withdrew from contact with the observer. They were observed,

usually, to be lying inactive in their cages, and when approached they would retreat into a corner. Three of the cats could be picked up and handled, although they would struggle and attempt to escape. The other cat in the group hissed when approached, lashed out with extended claws, and could not be picked up without heavy gloves. When stroked and petted, these cats remained quiet, became tense, and took every opportunity to escape. A light tail pinch resulted in a quick attack on the observer with extended claws, accompanied by a high-pitched wail. Even if the doors were open, these cats remained in the rear of their cage, occasionally coming out to the front, but never jumping on to the floor. When placed on the laboratory floor, they would immediately go to a secluded spot and hide. This group ate sparingly, leaving quantities of milk and meat in the dishes.

2. Behavior Following Bilateral Ablation of Amygdala.—For the first postoperative week these animals did not eat spontaneously, and it was necessary to force-feed them daily with milk and meat. They remained almost immobile in their cages, sitting in a sphinx-like position, unresponsive to external stimuli. Pinching them very strongly on the tail, however, gave rise to meowing and attempts at escape.

By the second postoperative week there was an increase in spontaneous activity, in comparison both with their preoperative behavior and with that seen in the normal stock cat. They would pace around the cage, rubbing against the walls and doors, and vocalize in a manner suggestive of a hunger cry in a normal cat. When the observer approached the cage, they would come to the front, tread with the front legs, and vocalize. When the door was opened, they jumped out of the cage. On being replaced in the cage, they would turn around and jump out again, and they repeated this performance any number of times. On the floor of the laboratory they wandered about, sniffed, licked, and investigated all the equipment and other animals in the room. They

were unusually attracted to moving objects, but quickly lost interest in one thing and then turned to something else. This type of behavior remained predominant throughout the observation period until placement of the second lesion.

Stroking and petting elicited purring and rubbing of head and body against the observer. Rolling over on its back, the cat would catch the experimenter's hand in its paws as he stroked its belly. It pawed, licked, and nipped his hand. The extent of this playful activity diminished somewhat during the sixth week but remained quite demonstrable until the second operation. Pinching the tail caused the cats to utter a weak cry, and they attempted to escape only when the stimulus became severe. They could be swung around in the air by the tail with impunity and purred and showed playful behavior when stroked and petted immediately afterward. In the presence of a dog they approached, sniffed, and licked him, then walked away, seemingly paying little attention to his barking. When mice were placed in their cages, they either played with them or ignored them completely. They never pounced on them directly, as did the hypothalamic cats.

They ate variable amounts of food, sometimes leaving portions and at other times consuming the entire daily ration. During a six-week period two cats showed an increase in weight; one showed no change, and the other lost weight.

3. Behavior Following Unilateral Ablation of the Amygdala.—There were no apparent changes observed in this cat following operation.

4. Behavior Following Hypothalamic Lesions.—The behavior of the three cats after the second lesion showed a gradual change in the direction of that seen in cats with only hypothalamic lesions combined with amygdala ablation (Group 1).

They ate spontaneously by the second postoperative day but were lethargic and did not move around much. They ate increasing amounts of food, and by the second

week they were consuming all of the daily ration. They continued lethargic and remained in the rear of the cage, with no concern for the activities around them. They assumed the crouching position and would not come forward when approached. When the cage door was left open, they would not come out, as they did previously. When placed on the floor they would go to a secluded spot and cower. They no longer responded to stroking and petting but would try to escape if restrained and attack. Pinching their tails evoked outbursts of hissing and savage attack, and they remained unapproachable for some time after. They would struggle when handled and attempted to bite if given the opportunity.

Spontaneous vocalization ceased; they no longer purred and would hiss with slight provocation. Licking and investigatory behavior, so prominent after the first lesion, were no longer present.

Comment

Following bilateral ablation of the amygdaloid complex and overlying cortex, our cats exhibited an increase in spontaneous motor activity, hypermetamorphosis, diminution of fear and aggression toward the observers, increased oral activity, raised threshold for noxious stimulation, and an increase in pleasure reactions to stroking and petting. The cat with the unilateral lesion showed no change. These results are in complete agreement with the previous cat studies of Schreiner and Kling, and Brady et al.^{5,20}

Viewed in total, the patterns of behavior exhibited in the cat following amygdala ablations bear a striking resemblance to the behavior of monkeys with similar or more extensive ablations.^{6,14,16,24} Work with rodents adds another order of animals in which similar results have been obtained.^{2,19} Although the extent of the individual components of the "amygdala syndrome" seems to vary among the various species, these differences may in time be explainable with advent of further knowledge of the natural behavioral patterns and central nervous or-

ganization of these animals. Variations in technique and type of observations, testing procedures, and extent of lesions are factors of inestimable importance that must be considered in evaluating the results of studies of this nature. Recent reports of studies of the human^{15,16} indicate that the role of the amygdaloid complex in the central organization of behavior is similar throughout the phylogenetic scale.

The behavior of our cats after bilateral lesions of the ventromedial hypothalamic nucleus and mammillary bodies is quite consistent with the reports of Wheatley,²⁴ Akert,³ and others.^{12,18} Our cats sustaining these lesions were characterized by a lowered threshold for tactile noxious stimulation, unprovoked savageness, increase in fear reactions, decrease in spontaneous motor activity, and hyperphagia.

Studies on the role of the ventromedial nucleus in behavioral mechanisms have been less extensive than those on the rhinencephalon. The excellent report of Wheatley on the effects of hypothalamic lesions in cats pointed to the ventromedial nucleus as the region where savageness and hyperphagia take place following its destruction. Similar results were obtained by Anand and Brobeck in the rat.²

Changes in Somatic Motor Activity.—The preoperative spontaneous motor activity was considerably diminished following the hypothalamic lesions. Following the amygdala ablation there was a transient increase for several days, but this soon disappeared and the animals reverted to their level of activity following the hypothalamic lesion. Similarly, the hyperactivity exhibited by the amygdal-ectomized cats was abolished by the placement of the diencephalic lesion. In addition, cats with hypothalamic lesions alone, or combined with amygdala ablations, exhibit a level of motor activity much below that seen in the normal cat. The increased motor activity, then, so characteristic of cats with amygdala ablations, appears dependent on the integrity of the ventromedial nucleus and mammillary bodies.

Affective Behavior.—The conversion of a previously docile, friendly cat to one which will attack with little or no provocation, and the failure of the amygdala ablation to modify this behavior indicate that, like the motor activity, the hypothalamus appears to dominate the behavioral changes produced by the amygdala lesions. Not only do the playfulness, docility, reduced fear responses, and raised threshold for noxious stimuli fail to appear if the ventromedial nucleus or the mammillary bodies have been previously damaged; but this group of changes can be abolished by the superimposition of the diencephalic lesions. Also, changes in feeding and vocalization appears to be dominated by the hypothalamus. The hyperphagia, so characteristic of cats with ventromedial lesions, was not influenced by amygdaloidectomy, while the increase in vocalization, seen in the amygdala preparations, was abolished by the subsequent diencephalic lesion.

These results indicate that the characteristic patterns of behavior, so dramatically produced in cats after electrolytic lesions of the hypothalamus, is in no way altered by a subsequent bilateral removal of the amygdaloid complex and surrounding structures. Furthermore, the behavioral symptoms produced in cats following bilateral ablation of the amygdaloid complex disappear after placing bilateral lesions in the ventromedial nucleus or mammillary bodies, and such animals show a form of the behavior typical of cats with hypothalamic lesions only.

Several factors may be considered in searching for an explanation of the above observations. It may be that the behavioral changes resulting from the hypothalamic lesions are simply dominant over those occurring after amygdaloidectomy. Or, on the basis of their anatomical and physiological relationships, mentioned below, they may be acting not in an independent but in a reciprocal fashion.

The main efferent pathway from the amygdala is the stria terminalis, which di-

vides into three components in the region of the anterior commissure. One component crosses to the amygdala of the other side; one continues rostrad to end in the septal area, and the third component goes to the hypothalamus—most likely to the ventromedial nucleus.¹ It is extremely likely that the septal component also reaches the hypothalamus via the medial forebrain bundle.

Anatomical evidence indicates that the ventromedial nucleus has connections with both the frontal areas and the dorsomedial nucleus of the thalamus.⁷ It is interesting to note that extensive lesions of the latter have induced alterations in behavior similar to, but less extreme than, those seen in cats with hypothalamic lesions.²⁰ Ablations of frontal areas, especially the orbital surface, have long been known to produce changes of a more complex nature, including rage reactions.

The afferents to the mammillary bodies are poorly defined and are probably composed of fibers from the mammillary peduncle, fornix, and medial forebrain bundle, with the main efferent passing up as the mammillothalamic tract to the anterior thalamic nucleus and thence to the cingulate gyrus. Experimental interruption of this system has resulted in behavioral changes which are in general of an opposite nature in cats and in monkeys.

Both the ventromedial nucleus and the mammillary bodies then probably receive impulses from the amygdala, which are then modified and relayed to the cortex via the thalamus. Whatever may be the role, then, that is carried out by the amygdala in maintaining adequate behavior of the organism, it appears that its action is primarily related to its hypothalamic connections, and possibly to other areas as yet unexplored.

Summary

In the cat the "amygdala syndrome" does not appear after bilateral ablation of the amygdaloid complex if there has been previous destruction of the ventromedial hypothalamic nuclei or the mammillary bod-

ies; and the amygdala syndrome, once produced by the amygdala ablation can be abolished by the hypothalamic lesions. Examples of lesions and theoretical considerations are included.

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Interrelations of Mesial Temporal and Orbital Frontal Areas of Man Revealed by Strychnine Spikes

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Strychnine neuronography¹ has been extensively applied to the study of the functional connections of different parts of the brain, but almost all this work has been done on animals. Species differences are so great that it seemed desirable to obtain information about the functional connections of the temporal lobe in man.

Material and Method

During temporal lobectomies for psychomotor epilepsy and combined temporal and frontal surgery for psychosis, "artificial" foci of spike-seizure activity were produced with strychnine in the frontal and temporal lobes of 34 patients. Of this group, 14 received injections of strychnine into the thalamus on one or both sides. The patients were anesthetized with thiopental (Pentothal) sodium, but in a few cases part of the study was done with local anesthesia, supplemented by pentobarbital (Nembutal) or secobarbital (Seconal) by mouth for basal sedation.

Strychnine (2% and 3%) was applied on small squares of filter paper, or 0.1 cc. was injected through one of the ports in a Grass needle electrode. This was accomplished by using the special hollow stylus included in the needle electrode. By this means fluids can be injected through the hole in any of the ring electrodes that are located at 1 cm. intervals along the shaft of the needle.

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Electroencephalographic recordings from the scalp and the depths of the brain were obtained in all cases. The recordings were made on four eight-channel Grass electroencephalographs. With this equipment it was possible to register activity simultaneously from 32 different areas on the surface of the head, the surface of the brain, and the depths of the brain. Recordings from the scalp were made with disc electrodes or with needle electrodes inserted into the scalp. For recordings from the surface of the brain, arrays of electrodes were made by stitching fine wires through heavy rubber sheeting (2 mm. thick), which had been cut previously into a suitable shape for placement on the exposed surface of the brain or for placement by means of retractors on the inferior mesial and lateral surfaces of the temporal and frontal lobes. Electrodes of this general type have been described and extensively used by Henry² and Marshall,³ but the rubber used in the present study was heavier than that recommended by Henry. Four to eight Grass multielectrode needles were used for recordings from the depths of the brain. The positions of the electrodes were verified by ventriculographic studies.⁴

Results

Spike discharges were easily produced with strychnine applied to the temporal and frontal cortex. When strychnine was injected into the white matter, seizure discharges could not be produced, except when the strychnine leaked along the shaft of the needle to reach the cortex. Spikes produced with local application of strychnine on the lateral surface of the temporal lobe usually remained sharply localized. However, on the mesial surface, after they reached full voltage, they commonly spread to the mesial orbital surface of the frontal lobe (Figs. 1A, 1B, and 1C) and to the tip of the temporal lobe. There was very slight spread to the lateral aspect of the midtemporal or posterior temporal region. Strychnine spikes that were initiated in the mesial temporal

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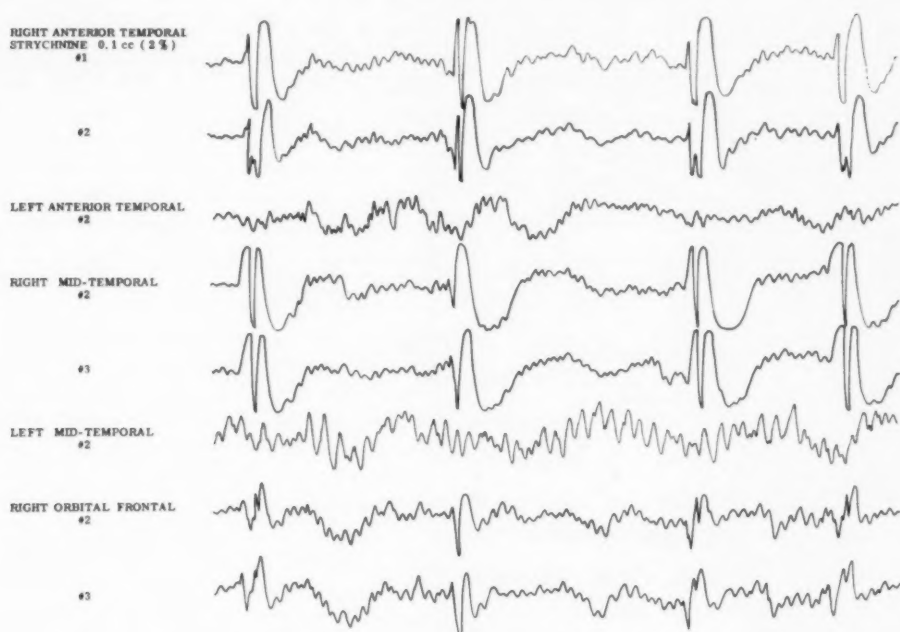


Fig. 1A.—Strychnine injected into the right mesial anterior temporal region through Electrode 1. The spike and slow-wave disturbance spreads to the right mesial temporal region and, to a less extent, to the right orbital frontal region; it does not show in the left mesial anterior temporal region. Needle and electrode positions are shown in Figure 1B. All recordings are monopolar to a reference electrode on the lobe of the left ear.

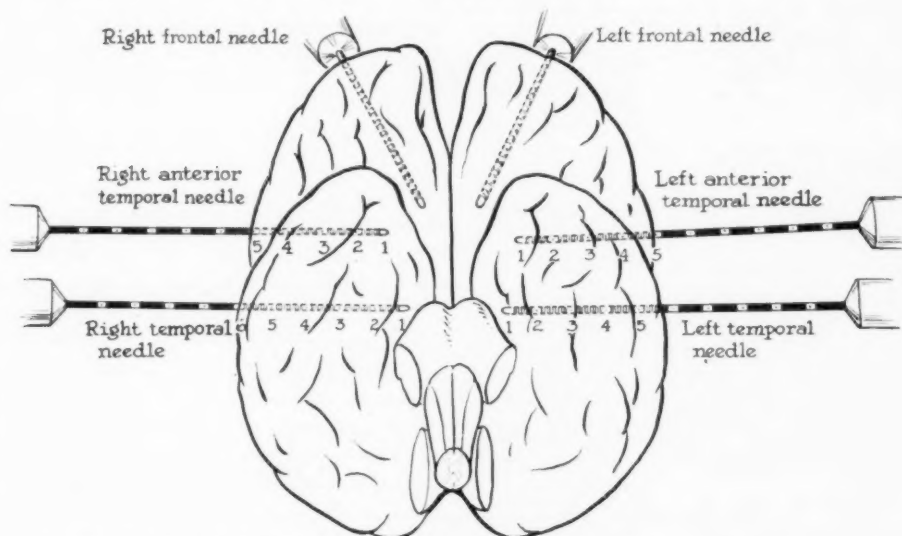


Fig. 1B.—Frontal needles are inserted into the posterior orbital surface of the frontal lobes. The anterior temporal needles are inserted through the tips of the temporal lobes, and the temporal needles, through the middle of the temporal lobes. In all cases, Electrode 1 is at the tip of the needle; Electrode 2 is 1 cm. farther back from the tip, and Electrode 3 is 2 cm. from the tip.

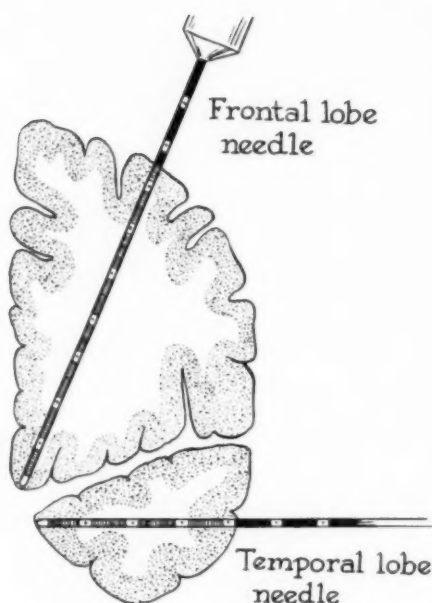


Fig. 1C.—Angle of insertion of frontal and temporal needles.

cortex spread to the mesial surface of the contralateral temporal lobe before they spread to the lateral surface of the ipsilateral temporal lobe. Spike discharges set up by local injections of strychnine into the mesial orbital surface of the frontal lobe (Figs. 2A and 2B) spread first to the ipsilateral mesial temporal cortex, to the contralateral mesial orbital frontal cortex, and, to a less extent, to the frontal poles. Only as part of a widening spread did the discharge appear in the ipsilateral lateral frontal cortex. Strychnine injected into the thalamus (Figs. 3A-B and 3C) did not produce local spike discharges. In only 1 trial out of 27 injections of strychnine into the thalamus was anything produced which could be identified even as questionable primary seizure activity in the thalamus.

Comment

In 1943 Bailey et al.⁵ reported their strychnine studies on primates, which revealed the functional connections between the frontal orbital cortex and the anterior

tip of the temporal lobe, and particularly the importance of the pathway afforded by the uncinate fasciculus. They stated that normally this pathway conducts only in one direction, from the orbital frontal cortex to the temporal lobe. This statement was corrected in the following year by Bailey et al.¹⁰ on the basis of further experiments. Their experience in animals was summarized by McCulloch.¹ Our studies confirm the spread of strychnine spikes from the anterior and mesial temporal lobe to the posterior and mesial portions of the orbital frontal cortex; and in our patients spread occurred in either direction, depending upon whether the strychnine was applied in the temporal or the frontal area. If strychnine was placed first in one and then the other, or if placed in the two simultaneously, spread of the discharges in both directions could be observed. In 1949 Petr et al.⁶ reported more fully on efferent intercortical connections of the temporal lobe, indicating that the tip of the temporal lobe is closely connected with the orbital frontal lobe. However, these workers did not discuss the connection between the mesial temporal lobe structures (uncus and hippocampus) and the orbital frontal lobe, which was observable in our patients. Pribram et al., in 1950,⁷ pointed out the connection of the periamygdaloid and hippocampal regions with the orbital frontal cortex. Their surmise that the probable connections were through the uncinate fasciculus is in general agreement with our findings, but they made it clear that other paths may also be present. Since our studies revealed a circuitous spread from one mesial temporal area to the ipsilateral mesial orbital frontal region, thence to the contralateral orbital frontal cortex, and thence to the contralateral mesial temporal regions, we can concur that most of the spread appears to take place through the fasciculus uncinatus. However, occasionally we noted spread from the anterior mesial temporal to the ipsilateral posterior mesial temporal and then into the contralateral mesial temporal region, as if spread

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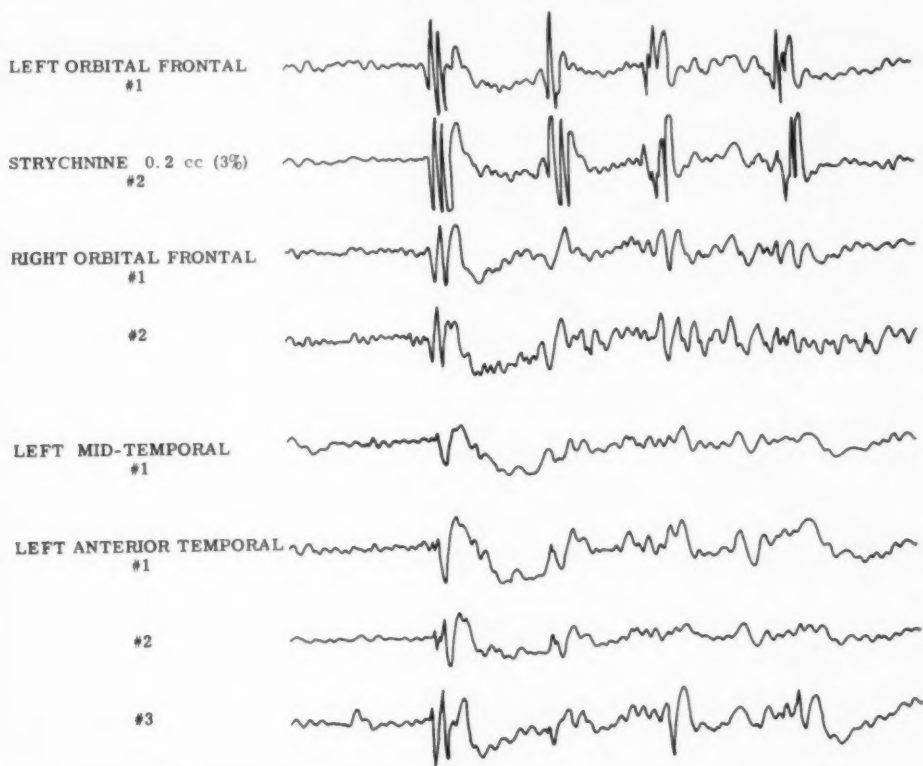


Fig. 2A.—Strychnine injected into the brain at Electrode 2 in the left orbital frontal area. Strychnine spikes spread to the right orbital frontal area and to the left mesial anterior temporal area. Left frontal and left anterior temporal (labeled temporal).

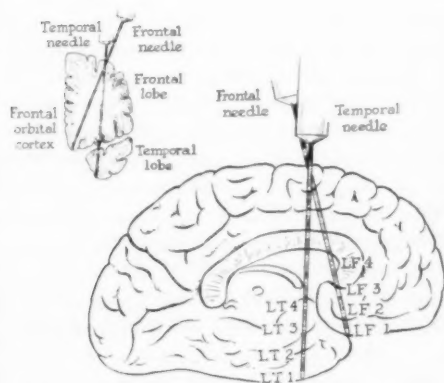


Fig. 2B.—Needle and electrode positions. Right frontal and right anterior temporal needles are in equivalent positions in the right hemisphere. The midtemporal needles are located as in Figure 1B.

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might have occurred through the fornices or some similar connection. This path is speculative, but at least some spread other than through the uncinate fasciculus must be postulated.

Our studies also point out several facts regarding the relationship of scalp, cortex, and depth recordings. Both strychnine and spontaneous discharges occurred in the deep infolded cortex and in the basal frontal and mesial temporal cortex which are not recorded as a significant change in the overlying scalp regions (Fig. 4). Also, a great deal of high-amplitude abnormality may be produced in the mesial cortex and at the base of the brain, or may occur spontaneously in these regions without any evidence

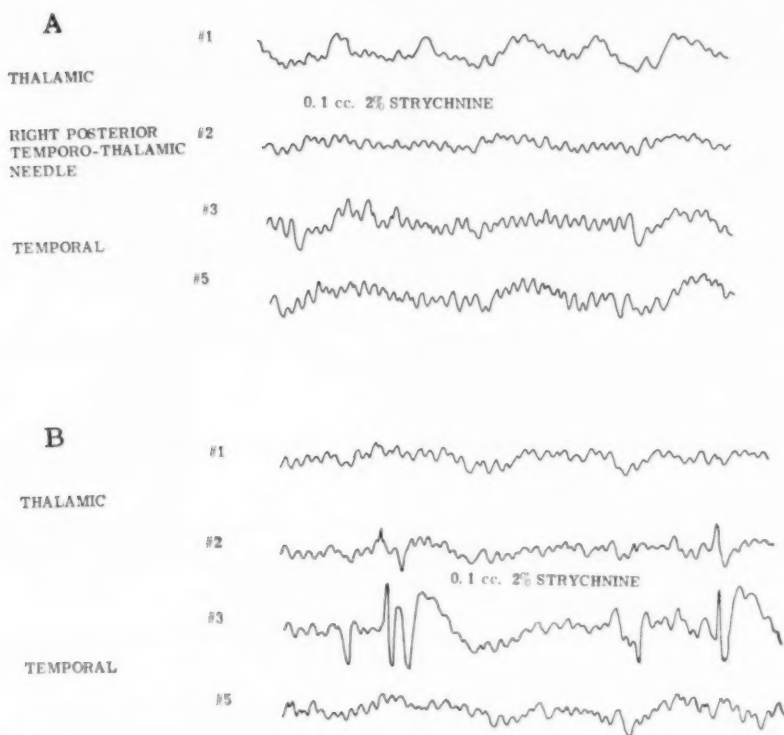


Fig. 3A-B.—(A) Strychnine injected at Electrode 1 into the region of the medial nucleus of the thalamus did not produce spike seizure activity. (B) Strychnine injected into Electrode 2, lateral to the medial nucleus of the thalamus, produced no seizure activity until it leaked back along the shaft of the needle to produce spikes in Electrode 3, which was in the mesial surface of the temporal lobe.

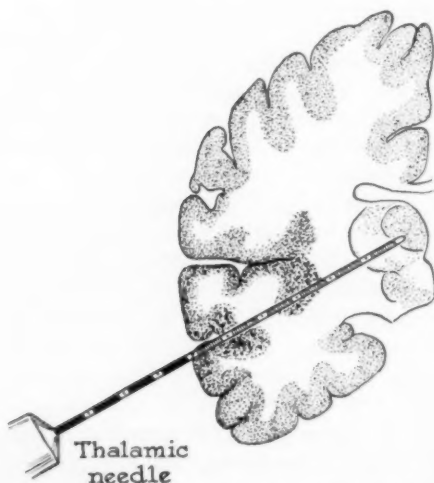


Fig. 3C.—Position of thalamic needle. Numbering of electrodes is the same as in Figure 1B.

of this disturbance appearing in recordings from the nasopharyngeal or tympanic electrode. It is important to realize that discharges of as high voltage as any that occur in epilepsy can be produced with strychnine in the mesial temporal and mesial orbital frontal areas without evidence of these discharges appearing on any external surface of the head. The findings are in agreement with similar reports of Hayne et al.⁸ and of Williams and Parsons-Smith.⁹

Our observations⁴ with depth recordings in psychomotor epileptics and psychotic patients revealed no evidence of spontaneous seizure activity in the thalamic region. The present study indicates that the thalamus is quite insensitive to strychnine, a substance which readily causes spike discharges when applied to the frontal and temporal cortex.

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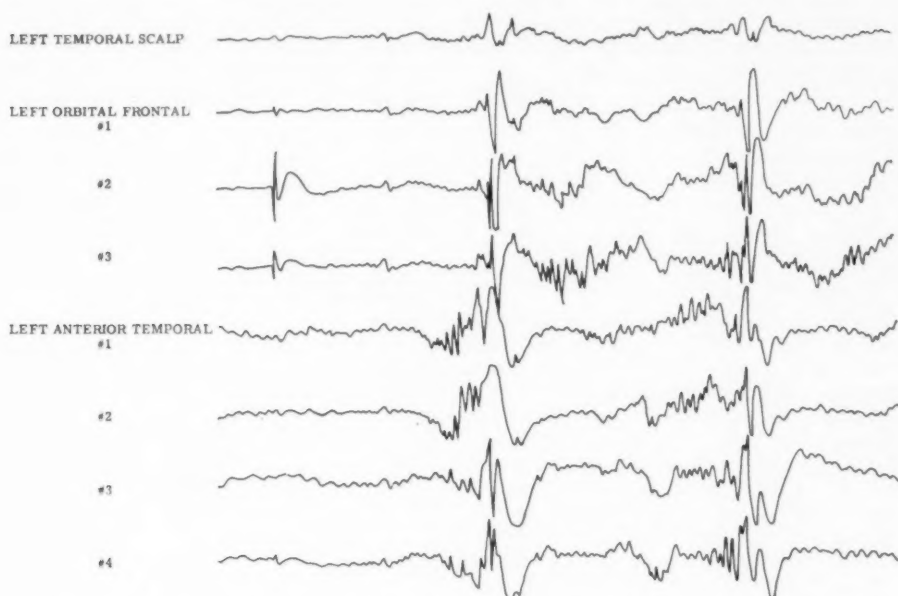


Fig. 4.—Spontaneous seizure activity involving the mesial temporal lobe and the orbital frontal area, showing feebly or not at all in the overlying temporal scalp recording. Needle and electrode positions as in Figure 1B.

Thus, we have been unable to find evidence that the thalamus plays a primary role in the production of the spike seizure activity which occurs in the frontal and temporal lobes of psychomotor epileptics and psychotic patients.

Summary and Conclusions

Three per cent strychnine applied to and injected into the temporal and frontal cortex produces spikes which spread in a manner that indicates a close functional relation between the mesial temporal and the mesial orbital frontal regions. These areas are more intimately connected with the mesial and anterior temporal areas on the same side and on the contralateral side than they are with the lateral midtemporal and lateral frontal areas. We have reported elsewhere⁴ that spontaneous seizure discharges in the mesial temporal region commonly spread to the mesial orbital frontal cortex and vice versa. Thus the observations reported here with strychnine are entirely in accord with

those obtained on patients with spontaneous seizure activity of the type that occurs in psychomotor epilepsy and/or psychosis.

Very high-voltage strychnine discharges can occur slightly below the surface of the cortex and not show in scalp recordings. Scalp recordings do not indicate reliably the presence or absence of seizure activity in the mesial temporal or orbital frontal areas.

Injections of 2% to 3% strychnine into the thalamic region did not produce spike discharges or any evidence of seizure activity. The same insensitivity to strychnine was observed in white matter.

Dr. Percival Bailey gave his encouragement and advice.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Nov. 20, 1956

Dr. Irving C. Sherman, President

Dr. Oscar Sugar, Secretary

Joint Meeting with the Chicago Ophthalmological Society

Retinal Artery Pressure in Diagnosis of Cerebrovascular Disease. DR. PAUL R. ROSENBLUTH.

Major brain stroke is the third most frequent cause of death in the United States, and 500,000 persons in this country sustain cerebrovascular "accidents" each year. The introduction of new diagnostic techniques has revealed many cases of vaguely classified neurologic disease, particularly in the young, to be of cerebrovascular origin.

Chiari, in 1905, first described temporary hemiparesis, aphasia, and loss of consciousness due to spontaneous occlusion of the carotid artery in the neck. Ramsey Hunt emphasized the importance of palpation of the carotid pulsation in patients with neurologic symptoms of vascular origin. It was not until 1937, however, that Ega Moniz was able to demonstrate nontraumatic thrombosis of the carotid in the neck by angiography. Carotid angiography in the presence of vascular insufficiency of the brain carries an inherent risk and may be disastrous. A safer method of demonstrating internal carotid patency makes use of the ophthalmodynamometer, a simple spring-gauge instrument used to compress the globe until the central retinal artery pressure is equaled. Pulsations in the artery then occur and can be observed with the ophthalmoscope.

Significant discrepancy in the pressure of one retinal artery as compared with its mate indicates obstruction to the internal carotid blood flow on the hypotensive side. The following information can be gained by use of this instrument: 1. Primary thrombosis of the carotid artery can be diagnosed. 2. Quantitative follow-up of results of carotid ligation in the treatment of intracranial aneurysm. The pressure distal to the ligation can be determined serially. 3. The Matas test can be quantitated and results of carotid ligation predicted before actual surgical ligation of the artery.

The technique is simple, harmless, grossly accurate, and painless, and a valuable adjunct to neurologic diagnosis.

Discussion

DR. DERRICK VAIL: This is a fine and exciting paper and should be of particular interest to ophthalmologists. At first glance the title is misleading, for the ophthalmodynamometer, introduced 30 years or so ago by Bailliart (1923) and others, has been utilized off and on by many workers, chiefly abroad, with the hope that it would help in interpreting and diagnosing lesions produced by cerebrovascular disease. It has not been widely accepted and utilized. Many of us in the 1920's and 1930's, enthused by Bailliart's book on the circulation of the eye, so ably translated by James Lebensohn, whom we are proud to have as one of us here, and purchasing his ophthalmodynamometers, tried out the instrument in collaboration with our neurologic colleagues. After a good trial, Dr. McIntyre, neurologist of Cincinnati, and myself felt that it was not particularly practicable and gave us little information that was trustworthy enough to be valuable in the diagnosis of diseases of the central nervous system. This conclusion was reached by many ophthalmologists, notably Streiff and Monier, whose book, "The Retinal Blood Pressure," published by Springer-Verlag, in Vienna, 1946, had a devastating effect, for it consisted of voluminous and extensive studies which tended to show that the measurement of the retinal artery blood pressure had no diagnostic value. Fortunately, however, hardier souls have persisted in their studies, and it is most gratifying to listen to one of them tonight. Dr. Rosenbluth's paper will renew our interest in this procedure, at least in the study of cases of suspected thrombosis of the carotid artery in the neck. For this reason, I think that the author's title should have been more specific. It then would have made us sit up and take more notice of it.

The syndrome of spontaneous closure of the internal carotid artery is one that is not particularly well known to ophthalmologists. In the paper by Walsh and King mentioned by the author, a reference is made to the review article by King and Langworthy (ARCH. NEUROL. & PSYCHIAT.

46:835, 1941) on this syndrome. They said that a thrombus which forms in the internal artery usually obliterates the lumen of the vessel quickly. When the artery is plugged by an embolus, a large thrombus quickly forms behind it, and the clot may extend down through the carotid artery. "After sudden spontaneous closure of the internal carotid artery, the patient," says Walsh, "according to our experience always becomes blind in the homolateral eye. It would appear likely that the process accounting for thrombosis in the carotid artery also occludes the ophthalmic artery. Ophthalmoscopic examination reveals primary atrophy of the optic nerve and pronounced diminution in the size of the retinal arteries."

Dr. Rosenbluth has, however, shown us the folly of using such words as "always" or "never" in medicine, by describing two proved cases in which optic atrophy and blindness did not occur, undoubtedly because of the good collateral circulation from the other side, which Walsh and King themselves described.

The author has shown us the value of this test, which is not difficult to perform, and not particularly dangerous if certain precautions are taken. It requires practice to perform it easily and quickly, before the ocular tension falls. It is of value in threatened occlusion of the carotid artery, particularly when the premonitory symptoms are fleeting and only suggestive. He finds it of value in estimating the safety of carotid ligature in cerebral aneurysms, presumably so in pulsating exophthalmos, and in estimating the prognosis, or at least the advisability, of endarterectomy in certain cases.

Besides the ophthalmodynamometers of Bailliart, there are other instruments which I think deserve mention as a list only. If you are interested, you will find such a list in a recent book by Bailliart (*Vascular Diseases of the Retina*, Paris, Gaston Doin & Cie, 1954, p. 51). These are:

1. Bliedung (1924)—a sort of bell jar over the orbit
2. Lundberg (1935)—annular compression tube to the limbus
3. Abramowicz (1927)—contact glass with rubber tube
4. Baumann (1929)—rubber hood for the globe and a mercury manometer
5. Uyemura and Suganuma (1934-1936)—similar to that of Bailliart
6. Kukan (1936)—a vacuum dynamometer
7. Linkz (1942)—a modified Kukan dynamometer
8. Spinelli (1934)—modified Bailliart instrument
9. Keil (1937)—Bailliart ophthalmodynamometer with weights

10. Sobanski (1936)—(combination of Bailliart ophthalmodynamometer and tonometer); measures ocular tension as well
11. Müller, Brüning, and Solhr (1938)—somewhat similar
12. Cattanes (1939)—measures pressure in vessels of bulbar conjunctiva
13. Baumann (1950)—newest, and may be the best. It is like a small manometer attached to a small rubber bag filled with glycerin. Its principle is that of two compressible spheres applied to each other so that the pressures are equal.

This extensive list tells us two things. First, that the subject is far from being discarded and, second, that the present instrumentation is not entirely satisfactory. It also means that further studies will no doubt continue.

I shall leave to Dr. James Lebensohn, pioneer worker with the Bailliart instrument, to tell us more about it, for he is our expert witness. I content myself with saying that the author has revived my interest in this field, and, since I possess an instrument, and have for many years, I shall dust it off and try again.

DR. JOSEPH E. ALFANO: One need not use the ophthalmodynamometer to determine when the pressure in the central retinal artery is lowered on the side of the thrombosed internal carotid artery. This may be determined by a very simple method, which consists of the following:

The globe on the inside of the uninvolved carotid artery is compressed with the index finger over the 12 o'clock meridian while the observer, using the ophthalmoscope, observes the ease with which the central retinal artery collapses on the surface of the disk as the globe is compressed by the finger.

The same procedure is performed on the involved side, and it is readily seen that, because of the reduced pressure in the central retinal artery from the involved side, the artery easily collapses as the index finger applies pressure to the globe.

DR. PAUL R. ROSENBLUTH: I appreciate Dr. Vail's discussion. I particularly left in the title the rather broad term of cerebrovascular disease, because I thought it would be well to emphasize the fact that cerebrovascular disease is a catch-all term, and that, before one should relegate a specific case to the limbo of cerebrovascular disease, it is well to think of internal carotid thrombus and at least examine the patient carefully for such thrombosis. Carotid thrombosis is increasingly being considered to occur as frequently as thrombus of a cerebral artery. Walker and Johnston, who collected 107 cases from the world literature, found optic atrophy and blindness in only a small percentage of their cases. In other words, the ophthalmic artery is nearly always spared. One does

not need to have atrophy and blindness and occlusion of the artery to make the diagnosis of internal carotid thrombosis.

Dr. Alfano is correct that the globe may be compressed with the finger. It is necessary to have the quantitative measurements in the two eyes for comparison, however.

Use of Angiography in the Study of the Visual Apparatus. DR. OSCAR SUGAR.

Vertebral and carotid angiograms were used to demonstrate pineal tumor compressing the corpora quadrigemina; arteriosclerosis of the posterior cerebral arteries, producing infarction of the visual cortex; arteriovenous malformation of the posterior cerebral distribution producing visual aphasia; occipital lobe tumors; hematoma of the temporal lobe from middle cerebral artery aneurysm; pituitary tumor; aneurysm of the communicating-anterior cerebral artery region compressing the optic nerves; meningioma of the tuberculum sellae, causing blindness; aneurysm of the internal carotid artery, producing third-nerve paralysis; carotid-cavernous fistulae, producing pulsating exophthalmos, and lesions within the orbit. The last-mentioned included aneurysm of the lacrimal artery, sarcoma, fibrosarcoma, neurofibroma, and dermoid tumors producing unilateral exophthalmos. With modern iodinated compounds, such as diatrizoate (Hypaque) (35% produces quite adequate visualization) and Renografin (38% and 48% solutions have both given excellent pictures), the dangers and complications of angiography are reduced to a point where this technique should be considered whenever diagnosis of a lesion of the visual apparatus within the cranium or outside the ocular bulb is in doubt.

DR. JOSEPH E. ALFANO: I should like to compliment Dr. Sugar on his excellent and comprehensive presentation of this subject matter, to which there is very little one might add.

I should, however, like to add a word of caution, for, while as ophthalmologists, neurologists, and neurosurgeons we are all agreed that arteriography of the internal carotid system may serve as an invaluable diagnostic aid, there are very definite indications and contraindications to its use. Arteriography should never be used in lieu of the complete ophthalmologic and neurologic examination, including the preliminary roentgenograms of the skull, both orbits, and optic foramina.

At the present time, the ophthalmological indications for cerebral arteriography appears to me to be the following:

1. Many undiagnosed neuro-ophthalmologic and neurologic problems, particularly when the pathology is considered to be in the anterior or middle cranial fossa.

2. Any patient who presents the signs and symptoms of the paratrigeminal syndrome. This syndrome consists of (a) pain along the course of the trigeminal nerve, (b) oculomotor nerve paralysis, and (c) altered (usually diminished) corneal sensation.

This syndrome is usually the result of a saccular aneurysm of the intracranial portion of the internal carotid artery. However, an identically similar picture may be produced by an aneurysm of the posterior communicating artery or an anomalous communication between the internal carotid and the basilar artery. This clinical picture also results from a tumor of the Gasserian ganglion, a meningioma of the petrous portion of the temporal bone, sarcoma of the base of the skull, a metastatic carcinoma to the base of the skull in the region of the Gasserian ganglion, and, lastly, a nasopharyngeal carcinoma which erodes the base of the skull in the region of the trigeminal ganglion.

3. Any unexplained exophthalmos, either pulsating or nonpulsating, particularly if unilateral, in which the usual exhaustive study has failed to uncover the etiology.

4. Many cases of intracranial (subarachnoid bleeding), particularly in younger persons.

5. Certain cerebral calcifications, particularly those small, fine spiral calcifications located in the occipital area, which may be indicative of a cerebral vascular malformation. Curved, thin, semicircular, suprasellar calcifications, which may indicate calcification in the wall of a suprasellar carotid aneurysm, call for arteriographic studies.

6. Certain intracranial tumors, particularly when exhaustive tests have failed to reveal the presence of or exact location of the tumor.

7. Ocular and systemic clinical pictures suggestive of a malformation or thrombotic occlusion of the internal carotid artery.

There are certain contraindications to arteriography, and these appear to be as follows:

1. In older patients, particularly those with arteriosclerosis and hypertension. Since there appears to be a greater incidence of complications, arteriography is frequently contraindicated.

2. Oftentimes arteriography may be contraindicated immediately after a severe bout of intracranial bleeding. However, on this point reliable observers seem to differ, for, according to some authors, it is in these cases that arteriography performs one of its greatest services.

Internal carotid arteriography may be associated with systemic and ocular complications.

Systemic complications reported in the literature are numerous and include urticaria, fever, local reactions in the neck, cervical sympathetic palsy with a resultant Horner's syndrome, recurrent laryngeal nerve paralysis, vomiting, hemiplegia (total or partial; transient or permanent), con-

vulsions, aphasia, air embolism, thrombosis of the internal carotid artery, and, rarely, a fatality.

These complications are thought to be due to cerebral vasospasm, with or without subsequent cerebral thrombosis. The spasm may be the result of irritation, allergy, or toxic effect of the dye and is more prone to occur in older persons with a compromised cerebrovascular system due to arteriosclerosis or hypertension or in younger persons with an anomalous cerebrovascular system.

These complications may be reduced by careful selection of patients, extensive experience of the angiographic team, newer contrast media, and slow injection of smaller amounts of the dye, and unilateral, instead of bilateral, arteriograms at the same sitting.

Treatment of these systemic complications may include dehydration of the patient, oral and intravenous vasodilators (in particular, papaverine), and repeated stellate ganglion blocks.

Ocular complications occurring after arteriography are multiple and varied and include the following:

1. Pain. The patient may complain of pain in and around the ipsilateral eye at the time of the injection of the dye, and this seems to indicate that the contrast medium has entered the internal carotid system. Walsh and Smith report a single case in which there was a complaint of a foreign-body sensation in the eye only during a few moments after each injection.

According to Schurr, the patient often describes a flash of light as the injection is being made, which he attributed to retinal irritation.

2. Pupillary changes. These have been observed in the homolateral eye in a minority of cases. Dilatation of the pupil occurs as the injection is being made, in possibly 25% of the cases. The dilatation is of brief duration, usually a matter of minutes or seconds, but may persist for hours. Narrowing of the pupil and hippus are also said to occur. Miosis of the contralateral pupil only has been observed by the author. Momentary narrowing of the retinal vessels during angiography occurs, according to Schurr, and is said to be followed by dilatation of the vessels.

3. Hemorrhages. These may occur in the skin, conjunctiva, and retina. These hemorrhages were commoner in the earlier reports and now appear in many cases to have been due to technical factors. The majority of the retinal hemorrhages were round, granular, and in a few instances preretinal. Most of the hemorrhages were confined to the posterior pole, with an occasional hemorrhage seen in the periphery. Many of the hemorrhages had white centers, and in many cases cotton-wool exudates were present.

4. Visual loss. Temporary visual loss, lasting from 10 to 30 minutes, has been observed, and

optic neuritis with eventual complete loss of vision has been known to occur.

Walsh and Smith described the case of a 60-year-old white man who awakened from a nap four hours after arteriography and found the vision in the homolateral eye reduced to hand movements. There was thought to be some edema of the macular area, but the retinal vessels were thought to be of normal caliber. A stellate ganglion block was done two hours after the visual loss was reported and repeated four hours later. At the time of the second block the vision was reported as improved, and on the following morning the visual acuity was 20/20 and the fundus appeared normal. The explanation for the visual loss may have been retinal spasm of the lodgment of the embolus.

Immediate loss of vision, which was considered to be the result of the development of bilateral homonymous hemianopsia, was reported by Walsh and Smith. The patient was a 24-year-old white woman who had 20/20 vision in each eye preoperatively. In order to fill the two carotids simultaneously, pressure was applied over the left carotid artery; as iodopyracet (Diodrast) was injected into the right carotid, within seconds, or at most within a minute, there developed total bilateral blindness, the pupils became semidilated and responded sluggishly to light, and the retinal arteries were said to have become narrowed but the disks and retina did not become pale. With 20 minutes after the onset of blindness, a stellate ganglion block was done on each side, and within a few minutes there was bare perception of light. Ten hours after the onset of blindness the patient described the sensation of grayness in the right homonymous half-fields. Within an additional 14-hour period there was return of function in the right half-fields. Twenty-four hours later, the visual fields of both eyes were full, and the visual acuity had reached normal levels in both eyes. Thirty-six hours after the loss of vision, the edema of the disks was as noted before, and all the retinal vessels appeared a trifle narrowed.

The authors suggest that bilateral filling of the internal carotid system by this maneuver is potentially dangerous. They feel that the bilateral homonymous hemianopsia was due to interference of a temporary nature with the blood supply of the visual pathways above the level of the external geniculate body.

They agree with Falls that the cause of these complications is not known but that they undoubtedly result from vascular changes secondary to allergic, toxic, or physical phenomena.

Picaza performed 50 angiographic studies in children and reported none of the complications seen in adults. There were no visual disturbances in these children, although three cases of Horner's

syndrome, due to damage to the cervical sympathetic nerve supply, were demonstrated.

A transient loss of vision following carotid angiography is reported by Atensek and Markham. Immediately after the last injection of iodopyracet, the patient complained of burning of the right side of the face and slight supraorbital ache. Two hours later he discovered that the vision in the right eye was impaired and he could distinguish only large objects. Four hours after the injections the visual acuity was reduced to counting fingers. Fundus examination revealed the right disk to be of normal color, with some blurring of the disk margin superiorly and nasally. The arteries and veins were normal, although some macular edema was present. The left fundus was similar except for the absence of macular edema. Peripheral fields were generally contracted, being more so on the nasal side. There was a large contracecal scotoma to a 5 mm. white object at 1 ft. Six hours after the angiography, the vision was unimproved, and a stellate ganglion block using 1% procaine hydrochloride was done. Thirty minutes later the patient volunteered that his vision was improving. Sixteen hours after angiography he could read large letters and the scotoma was reduced in size. Another stellate ganglion block was performed. Twenty-one hours after the onset of visual symptoms the scotoma was no longer present, the visual acuity had returned to 20/40, and there was a decrease in the edema of the macula areas. A third stellate ganglion block was done, and 48 hours after the onset of the visual disorders, central and peripheral fields and the fundi were normal.

Weekers reported a case of occlusion of a retinal artery following cerebral angiography. Twenty-four hours after angiography the patient noticed a superior field defect in the right eye. The visual field showed a superior nasal quadrant defect, and examination of the fundus revealed edema of the macular area. Weekers considers that embolism was most likely responsible and due to a floating blood clot, fragment of tissue, or dislodged atheromatous plaque.

In closing, I should like to say that arteriography is proving to be a valuable diagnostic tool and, if used wisely, will continue to be so.

QUESTION: What precautions are taken when this is done?

DR. OSCAR SUGAR: One of the things is not to use iodopyracet. This substance, which has been used for many years, is much more toxic than the more modern dyes, such as diatrizoate (Hypaque). These newer drugs produce no pupillary dilatation. We have not found an ocular complication in the last 200 cases. There have been no deaths in the last 200 cases, in which the newer dye was used. We use as little dye as possible. All the films may be taken with the new machine with one injection of dye. The more we become used to these machines, the fewer injections are used. It can be quite safe.

QUESTION: A few of these older patients looked to be in the arteriosclerotic age. If their problem is diagnosed, would they be subjected to a more benign treatment procedure? I should also ask whether you would subject some of these patients with cavernous-sinus, arteriovenous fistulas to these procedures, and whether it is pertinent to diagnose and treat them.

DR. OSCAR SUGAR: From my standpoint, there are only two treatments for cavernous-sinus fistula: one is to do nothing, and the other is to tie off the carotid artery. If you are going to do nothing, you do not need to make any tests. If you are going to tie off the carotid artery, you should do arteriography. You do not need to fear doing damage because the patient is not already hemiplegic, meaning there is adequate collateral circulation. I have had no trouble in that type of case after arteriography.

DR. IRVING C. SHERMAN: When you demonstrate an aneurysm on one side, presumably on the side where the clinical phenomena exists, and you go ahead and tie off the internal carotid artery, how sure are you that there is no aneurysm on the other side?

DR. OSCAR SUGAR: The statistics are that about 10% of aneurysms are bilateral or multiple. We do angiograms on both sides to make sure there is no aneurysm on the opposite side. Sometimes there are two or three. Dr. Paul Bucy had one in which there were three aneurysms. This has happened once to me also, and to other people as well. When you do not find more than one, you are lucky. When you find multiple ones, there may be no localizing signs to tell you which one bled. Some people do vertebral arteriography to see whether there are other lesions, and some do not.

Abstracts from Current Literature

Edited by Dr. Bernard J. Alpers

Diseases of the Brain

INFECTIOUS DISEASES: ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS. H. A. REIMANN, A. M. A. Arch. Int. Med. 98:639 (Nov.) 1956.

Reimann stresses a number of recent developments of neurologic interest in this comprehensive review of progress in the field of infectious diseases. The generally unrecognized high incidence of myocarditis in poliomyelitis (present in 14 out of 15 autopsied cases recently studied) is mentioned, and the occasional masking of neurologic symptoms by those of acute cardiac disease, as occurred in one instance, is cited. Research with chemotherapeutic agents for poliomyelitis progresses, and the effectiveness of 4-amino-1-naphthol HCl and gallic acid in the prophylaxis and treatment of the disease in monkeys is mentioned. There is now an effective colorimetric test for virus and antibody by the measurement of degree of inhibition of the yellow color of HeLa cell cultures treated with phenolsulfonphthalein in the presence of unneutralized virus. Another approach utilizes the "biological interference" phenomenon (previously noted empirically in the apparent deterrent effect of vaccinia on poliomyelitis virus), wherein increasing cellular resistance to the poliomyelitis virus occurs after exposure to the Newcastle virus. Relatively high incidences of mortality (25%) and sequelae (45%) of measles encephalitis are reported. The incidence of this complication of measles is 1 in 1300. Herpes simplex is responsible for 5% of meningoencephalitis—less than leptospiral meningoencephalitis (7%), lymphocytic choriomeningitis (9%), and mumps (12%). The development of a fatal myocarditis is a frequent feature of the Group B Type 3 Coxsackie virus.

Insofar as bacterial diseases are concerned, the value of supplementation of antimicrobial therapy of tuberculous meningitis by cortisone or corticotropin seems to be established. These agents effectively reduce cellular reaction and subsequent fibrosis, with a marked decrease in residual neurological derangements (one in six cases with supplemental hormone therapy, as compared with three in six cases with antimicrobial therapy alone). Pneumococcal meningitis maintains a high mortality rate (45%) with optimal therapy and is now more frequently associated with middle ear foci than with pneumonia. The control of spasms in tetanus by the combination of barbiturates and chlorpromazine is reported. The author advises prophylactic use, not only of antitoxin but also of antimicrobial preparations (penicillin and/or oxytetracycline) administered within 24 to 48 hours after the injection. Dangers in the administration of pertussis vaccine are pointed up by the report of an instance of encephalomyelitis following vaccination. An electroencephalographic study prior to and following vaccination disclosed the production of distinct electroencephalographic abnormalities in two of a group of 33 vaccinated children.

The incidence of neurologic complications in histoplasmosis is higher than is generally recognized, lesions of the brain or meninges, being shown in a group of 11 cases with autopsy. The significance of the treponemal immobilization test in syphilis is discussed. Its unique value would seem to consist of the elimination of false positives (obtained from older standard tests) in the diagnosis of latent asymptomatic syphilis.

PARSONS, Montrose, N. Y.

EMBOLI ARISING IN THE LUNGS. R. WALLACH, N. POMERANTZ, and D. DiMAIO, A. M. A. Arch. Int. Med. 99:142 (Jan.) 1957.

The authors report the case of a 23-year-old patient who developed congestive heart failure (left ventricular) complicated by right flaccid hemiparesis, resulting in a fatal issue despite treatment with antibiotics, anticoagulants, and corticotropin. A clinical diagnosis of chronic rheumatic heart disease with subacute bacterial endocarditis and cerebral embolism was made. Autopsy findings disclosed no valvular vegetations, mural thrombi, or patent foramen ovale. Dissection of the smaller pulmonary veins in the region of a pneumonic focus in the right lower lobe disclosed extensive thrombosis, which was considered to constitute the source of the embolus. Unfortunately, no mention of autopsy findings involving the central nervous system was made. Conditions resulting in pulmonary venous thrombosis include bronchiectasis, broncho-

ABSTRACTS FROM CURRENT LITERATURE

genic carcinoma, pulmonary infarction, and pneumonia. The authors stress the importance of investigation of the lesser pulmonary veins in determining the source of systemic emboli in cases in which no intracardiac pathology is manifest.

PARSONS, Montrose, N. Y.

ACUTE SPONTANEOUS CEREBRAL VASCULAR ACCIDENTS IN YOUNG NORMOTENSIVE ADULTS.

B. E. SPROFKIN and H. H. BLAKEY, A. M. A. Arch. Int. Med. 96:617 (Nov.) 1956.

Sproffkin and Blakey review the literature with respect to cerebral vascular accidents occurring in persons below the age of 40, which comprise less than 5% of all such accidents. They report 18 cases of such syndromes: 1 case each of lupus erythematosus and scleroderma; 2 each of thromboangiitis obliterans and vascular syphilis, and 1 of postpartum cerebral venous thrombosis, which, along with 5 cases diagnosed as "thrombosis of the middle cerebral artery due to unknown cause," probably representing instances of spontaneous thrombosis of the internal carotid artery, were responsible for 12 instances of cerebral thrombosis. Thrombocytopenic purpura and fibrinogenopenia of pregnancy, along with one case each of angiomatous malformation and "spontaneous subcortical hematoma of obscure etiology" comprised four instances of cerebral hemorrhage. One case each of subacute bacterial endocarditis and postmeasles encephalopathy completed the series. The authors mention other causes of cerebral vascular accidents due to thrombosis in young persons, such as sickle-cell disease, polycythemia vera, neoplastic compression of a vessel, ergotism, migraine, carbon monoxide poisoning, and malaria. They stress the relative infrequency of syphilis as a cause of thrombosis in younger persons since the penicillin era and conclude that premature atherosclerosis constitutes the main etiologic factor in spontaneous cerebral vascular accidents in young normotensive adults. Additional causes of cerebral hemorrhage in young patients include hemophilia, hypoprothrombinemia, rupture of saccular basal aneurysms and hemorrhagic encephalopathy occurring during the acute phases of various infections, such as measles, pertussis, diphtheria, and typhus. Fat and air emboli, the Libman-Sacks manifestations of lupus erythematosus, and myocardial infarction with detachment of a mural thrombus in the presence of sudden alteration of cardiac rhythm constitute additional causes of cerebral embolism.

PARSONS, Montrose N. Y.

INFECTIOUS DISEASES: ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS. H. A. REIMANN, A. M. A. Arch. Int. Med. 99:955 (June) 1957.

The author stresses a number of recent developments of neurological interest in this review of progress in the field of infectious diseases. The indiscriminate use of antimicrobial agents, resulting in an increase in incidence of drug-resistant infections, notably staphylococcal, is extensively discussed, and reports of the development of meningococcal meningitis in several patients being treated with penicillin for other conditions are cited. In 50% of these cases of meningococcal meningitis complications developed, and two-thirds of the deaths were due to the Waterhouse-Friderichsen syndrome (50% fatality rate), resistive to treatment with antimicrobials, arterenol, and adrenocorticoid agents.

The widespread distribution and highly contagious character of poliomyelitis are emphasized in a study based on the use of complement-fixation tests of contacts. A British investigation established the fact that diphtheria-pertussis vaccination not only predisposes to the development of poliomyelitis but also influences selection of the site of paralysis. The potential danger of the use of attenuated vaccines was experimentally demonstrated in inoculated monkeys which developed paralysis. Virological studies revealed a reversion to highly virulent strains. The risks attendant upon oral administration of attenuated virus are greater, as Irish investigators revealed in a study demonstrating the presence of excreted virus in the stools of successfully (good antibody formation with no morbidity) inoculated persons, thus facilitating further dissemination. A new flocculation (virus-antibody) micro test for poliomyelitis virus typing and assay is described, and the prophylactic value of helenin in monkeys is demonstrated. A new clinical antibody termed "benign, myalgic encephalomyelitis" is described. It is characterized by exanthem, fever, myalgia with paresis, involvement of the reticuloendothelial system with lymphadenopathy, emotional residuals, signs of meningeal irritation in the presence of normal spinal fluid, and a protracted course with generally favorable outcome. Distribution is widespread and epidemic in character. The etiology is obscure; poliomyelitis, Coxsackie virus, or other known viruses are excluded, and the possibility of

the causative role of one or another of the ECHO viruses, especially Type 9, associated with some cases of so-called aseptic meningitis, is considered. This latter group of viruses may also be responsible for cases of Gerlier's "epidemic vertigo" and the recent British outbreak of "winter vomiting" with vertigo and cerebrospinal fluid pleocytosis.

A less dangerous antirabic vaccine prepared in duck eggs is reported. Discovery of the rabid infestation of several species of southern bats constituted the basis for treatment of all bat bites as cases of exposure to rabies. Myocardial involvement is a feature of encephalomyelitis due to a number of viral agents, including Columbia SK, MM, African Mengo, and Coxsackie viruses, and this is a particular risk in the event that cortisone is given in cases of benign Coxsackie disease. The latter was demonstrated experimentally in mice, wherein extensive myocardial necrosis succeeded cortisone administration. This and other hazards attendant upon the use of cortisone in viral disease are stressed. A case of meningo-encephalitis with atypical lymphocytes and heterophil antibody in the spinal fluid and blood following prefrontal leucotomy is reported. Cautious use of cortisone is said to have been beneficial in this case.

Epidemiologic studies of leprosy have disclosed it to be more contagious than supposed, although its incidence is dropping owing to more general use of sulfone therapy. Most lepers die of amyloidosis, and all show renal involvement. Electron microscopy methods permit rapid morphological distinction of *M. lepra* and *M. tuberculosis* organisms. A Brazilian study of 700 cases of tetanus treated with antimicrobial agents, antitoxin, continuous intravenous mephenesin (Tolserol), and sedation showed a mortality rate of 18%, as contrasted with one of 27% when antitoxin and sedatives were used alone.

The recently developed Treponema-pallidum-immune adherence test is said to be cheaper and simpler than the immobilization (TPI) test and equally reliable. The similarity of African trypanosomiasis to syphilis in the production of central nervous system lesions is emphasized, and a case of the development of the adiposogenital syndrome in a patient with trypanosomiasis is described. A previously unrecognized high incidence (30%-70% of persons 40 to 60 years of age) of toxoplasmosis was revealed by screening of normal persons by the use of skin and serologic tests. Undercooked pork was found to be the source of infection. The low incidence of morbidity is thought to be related to the action of specific antibody developed through an adequately functioning properdin defense system.

PARSONS, Montrose, N. Y.

THALAMIC SYNDROME DUE TO CEREBRAL EMBOLISM IN RHEUMATIC HEART DISEASE: SUCCESSFUL TREATMENT WITH CORTISONE. A. DE VRIES, B. BORNSTEIN, and E. FRIEDMAN, A. M. A. Arch. Int. Med. 99:1001 (June) 1957.

The authors describe the case of a middle-aged housewife with a childhood history of rheumatic fever followed by chronic cardiac involvement, who experienced the sudden onset of minimal left hemiparesis (including the face), transitory pain at the tip of the tongue, and persistent spontaneous pain, hyperpathia, and dysesthesia of the left fingers. The fingers exhibited skin and nail changes suggestive of "reflex sympathetic dystrophy." During the first month of hospitalization the complaints of pain in the fingers were minimally relieved by generous amounts of sedatives, analgetics, and narcotics, whereupon cortisone, 300 mg. per day, was given. Within two days a marked reduction of pain was noted, and within a week the symptoms had completely disappeared. At the end of a month treatment was discontinued without recrudescence of pain, and within six months the appearance of the fingers had become normal.

The authors hypothesize an embolus stemming from rheumatic-heart-valve vegetation and proceeding to the branches of the thalamogeniculate arteries supplying the medial portion of the nucleus ventralis posterior and giving rise to the rather sharply defined cheiro-oral thalamic syndrome shown by this patient. The rationale for the therapeutic efficacy of cortisone in this case is obscure, but the authors state that it was not on the basis of euphoria and suggest that its action may have been similar to that seen in its effective use in cases of causalgia, shoulder-hand syndrome, and other instances of sympathetic reflex dystrophy.

PARSONS, Montrose, N. Y.

DERMATOMYOSITIS—A REVIEW OF NINETEEN CASES IN ADOLESCENTS AND CHILDREN. M. A. EVERETT and A. C. CURTIS, A. M. A. Arch. Int. Med. 100:70 (July) 1957.

Sixty patients with dermatomyositis were studied during a 20-year period at a large teaching hospital. Everett and Curtis review the clinical and pathologic features of 19 patients between

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4 months and 17 years of age. The most frequent presenting symptom was the "butterfly" type of facial erythema. The commonest physical findings were this type of erythema, localized muscular pain, low-grade fever, induration, contractures, and poikilothermia. Arthralgia and generalized muscular weakness were not encountered, and gastrointestinal or cardiorespiratory involvement, calcinosis, and hepatomegaly were seen in less than one-third of cases. About 40% of patients gave a history of aggravation of symptoms upon exposure to sunlight. Laboratory abnormalities were confined to increased urinary creatine, occasional elevated sedimentation rate, and mild eosinophilia. There was no instance of the positive L. E.-cell phenomenon. The barium swallow test revealed hypopharyngeal paresis in over one-third of cases and constituted a fairly reliable sign of unfavorable prognosis. Biopsy findings included all stages of focal muscular involvement, from mild perivascular infiltration, increase in interstitial nuclei, and lymphorrhagia to necrosis, fibrosis and calcification. There was no involvement of vessel walls. Fatal cases exhibited similar involvement of cardiac and pharyngeal muscles. Half of the cases showed skin changes, mainly atrophy. There were no instances of associated malignancy. Patients were treated with para-amino benzoic acid, vitamin E, and corticotropin and/or cortisone derivatives. Aside from some subjective improvement and non-specific anti-inflammatory effects from the latter preparations, no benefit was realized. Early adequate physical therapy was significant in correcting or preventing contracture deformities. Over one-half (11 patients) died, 20% within the first year, as a result of bulbar or cardiac involvement, and the remainder, of intercurrent infections within the first five years. Most patients who survived three years (eight patients) experienced no further progress of the disease. Half of these had advanced calcinosis and are severely crippled; the remaining 20% are well. No remissions or exacerbations occurred.

PARSONS, Montrose, N. Y.

CENTRAL NERVOUS SYSTEM SARCOIDOSIS SUCCESSFULLY TREATED WITH PREDNISONE. D. P. FITZPATRICK and G. E. EWART, A. M. A. Arch. Int. Med. 100:139 (July) 1957.

Fitzpatrick and Ewart report the case of a 32-year-old Negro man admitted in a comatose hemiparetic condition suggestive of meningoencephalitis, with lymphocytosis and increased protein in the spinal fluid. He was placed on isoniazid, streptomycin, and aminosalicylic acid U.S.P. After several months of improvement, with increasing alertness and resolving hemiparesis, he complained of increasing headache and became delirious, febrile, and somnolent. A combination of features, including marked enlargement of the hilar nodes as seen by x-ray, 10% eosinophilia, inversion of the A:G ratio, and negative tuberculin tests in the presence of persistent spinal fluid changes, suggested the possibility of sarcoidosis. The diagnosis was confirmed by a scalene lymph node biopsy. The patient's course continued downhill until the institution of prednisone (started at 80 mg. per day), four days after which definite improvement was noted. Symptoms recurred upon its temporary withdrawal. Complete recovery while on prednisone took place over a nine-month period, at the end of which time a spinal fluid protein of 76 mg. per 100 cc. was the only significant abnormality. The authors stress the importance of considering the possibility of sarcoidosis in patients with coma, convulsions, increased intracranial pressure, or hypopituitarism if there is lymphadenopathy, spleno- or hepatomegaly, skin or eye lesions, a negative second-strength tuberculin test, pulmonary infiltrations, joint deformities of hands or feet, and EKG changes. An histologic diagnosis of sarcoidosis should be promptly succeeded by steroid therapy.

PARSONS, Montrose, N. Y.

ACQUIRED TOXOPLASMOSIS. A. D. HOOPER, A. M. A. Arch. Path. 64:1 (July) 1957.

Hooper reports the case of a 43-year-old man who died with toxoplasmosis. He had had a long history of panhypopituitarism, and a chromophobe adenoma had been removed 10 years before. His terminal illness began with frequent frontal headaches, narcolepsy, cough, and coryza, and he was admitted to the hospital because of hematemesis and tarry stools. There was clinical evidence of hypopituitarism; the heart and spleen were enlarged, and the optic disks were pale. There were no signs of meningeal irritation and no localizing neurologic signs. He was discharged after blood transfusions were given, but the narcolepsy and tarry stools persisted. He was readmitted about three months later because of the gradual development of coma over a 12-hour period following the onset of a sore throat and fever. Again, there were no localizing neurologic signs. A lumbar puncture yielded xanthochromic fluid (5650 red blood cells) with no white cells, and a total protein of 45 mg. per 100 cc.

Cultures of blood, urine, and cerebrospinal fluid were negative. The patient recovered consciousness on the following day and was again discharged. Cortisone was given to control a bleeding tendency, and penicillin and streptomycin were given as well. He was readmitted 10 days later because of abdominal distention, dyspnea, and confusion. There were many subcutaneous hematomas, and the liver was enlarged, as well as the spleen. The temperature ranged between normal and 105 F. The cerebrospinal fluid was completely normal except for a pressure of 330 mm. Terminally, he developed ankle clonus and diminished reflexes on the right and died six days after his final admission.

Autopsy showed that the heart was enlarged, with subendocardial petechiae. The spleen weighed 800 gm. The liver was cirrhotic, with a fine nodularity. The brain appeared normal except for the residual of the old craniotomy and tumor removal. Microscopically, the pseudocysts of *Toxoplasma gondii* were found in the heart, lung, thyroid, stomach, retroperitoneal fat, bone marrow, and skeletal muscle. Scattered throughout the brain and spinal cord were small microglial nodules with necrotic centers, but only rarely was a pseudocyst found in such foci. On the other hand, there were numerous pseudocysts in the brain and cord without surrounding cellular reaction. No organisms were found in the scar tissue of the old operation.

A brief review is given of the autopsy findings in 21 published cases of adult toxoplasmosis. The author points out that most of the cases have had neurologic involvement and that the neurologic affection is almost always the cause of death.

Foley, Boston.

RELATIONSHIPS OF CEREBRAL DISORDER TO FAULTS IN DENTAL ENAMEL. W. F. VIA JR. and J. A. CHURCHILL, A. M. A. J. Dis. Child. 94:137 (Aug.) 1957.

Via and Churchill studied the relationship of cerebral disorders in children to hypoplasia of dental enamel. Since the chronological pattern of the growth of enamel is known, it was possible to estimate the time when the cerebral disorder was established.

Hypoplasia of the enamel is characterized by a grooved ring about the crown of the tooth. Hypoplasia was considered to have occurred in prenatal time when the defects were present on the incisal four-fifths of the primary central and lateral incisors. Defects were considered to have occurred in the neonatal period when they were observed one-third of the way from the cusp tips to the cervical line of the crowns of the first primary molars.

The incidence of enamel hypoplasia was found to be 68% in children with congenital disorders of all types, as compared with 10% in normal children, a significant statistical difference. Athetosis and spastic diplegia were uniformly associated with enamel defects. There was a correspondence between the time of occurrence of these enamel defects and the potentially brain-damaging events in 44 of 66 abnormal children.

Siekert, Rochester, Minn.

SIMULTANEOUS OCCURRENCE OF MONGOLISM AND LEUKEMIA. W. KRIVIT and R. A. GOOD, A. M. A. J. Dis. Child. 94:289 (Sept.) 1957.

A nation-wide survey revealed that the actual occurrence of simultaneous leukemia and mongolism was approximately three times as high as that which might be anticipated from chance association and that this difference was statistically significant. Congenital leukemia was nine times as high among newborn mongoloid infants as that of all leukemias in children up to 4 years of age. The reasons for these associations are apparently not known, although a common factor is implied.

Siekert, Rochester, Minn.

A CASE OF LINDAU'S DISEASE SIMULATING ANOREXIA NERVOSA. E. J. LIEBNER, Am. J. Roentgenol. 78:283 (Aug.) 1957.

Liebner discusses the case of a 28-year-old woman who was referred for roentgen examination of the upper gastrointestinal tract because of a six-year history of hiccups, weight loss, epigastric distress, anorexia, and frequent morning vomiting. The patient was thought to have anorexia nervosa because of the long history of the disease and because no organic cause for her symptoms had ever been found in previous studies. The only new symptoms she presented were sensations of dizziness associated with blurring of vision and loss of balance. Physical examination showed a visible bulge in the left upper quadrant of the abdomen and a firm, slightly irregular, tender mass in this region. Roentgenographic study of the upper gastrointestinal tract showed displacement of the stomach and the duodenal loop. A large pancreatic

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cyst was suspected as the probable cause of the displacement. At operation a multicystic pancreas was found. The spleen and most of the pancreas were removed. The operation did not relieve the patient's distressing symptoms.

After neurological examination a cerebral ventriculographic study was performed. This showed symmetrical dilatation of the lateral and third ventricles without displacement of the ventricles. The aqueduct of Sylvius was dilated. Ophthalmoscopic examination showed no abnormality of the retinas. A craniotomy was performed. A large anomalous blood vessel was found crossing the vermis and terminating in a mass of closely interwoven blood vessels which filled the fourth ventricle. On both sides of the angiomatous mass were large cysts. The patient died six days after operation. Postmortem study demonstrated the large vascular mass in the region of the brain stem, softening of the medullary region of the brain, and adrenal rests in the kidneys. Microscopic study of the tissues removed at operation and at autopsy showed that the vascular tumor in the fourth ventricle was an hemangioblastoma and that the pancreas was involved with polycystic disease.

Lindau's disease consists of cystic hemangioblastomas of the cerebellum and of the retina, frequently associated with cystic disease of the kidneys and pancreas. The disease was overlooked for six years in this case, probably because of the absence of neurological symptoms during most of that time, the absence of symptoms of pancreatic-enzyme deficiency, and the absence of lesions of the retina.

WEILAND, Grove City, Pa.

LEFT HEMIPLEGIA AND MOTOR IMPERSISTENCE. M. FISHER, *J. Nerv. & Ment. Dis.* 123:201 (March) 1956.

Fisher observed that 10 patients who sustained right cerebral vascular lesions with consequent left hemiplegia had an inability to maintain or persist in the execution of certain movements. The most readily detected change was the inability to keep the eyes closed or the tongue protruded for more than a few seconds. There also occurred an inability to maintain the mouth open, to keep the eyes fixed centrally and to avoid their being attracted from this position by visual stimuli, as well as difficulty in sustained breath holding. These disturbances were most apparent immediately after the ictus and tended to subside as the patient improved. There was some degree of mental impairment. A group of 30 dextroplegics with dysphasia did not exhibit these defects.

The author concludes that motor impersistence might be regarded as failure to maintain a motor set, that this is associated with some impairment of mentation, and that the syndrome is usually the result of lesion of the nondominant cerebral hemisphere.

BERLIN, New York.

COMMUNICATING HYDROCEPHALUS FROM SUBARACHNOID BLEEDING. E. L. FOLTZ and A. A. WARD JR., *J. Neurosurg.* 13:546 (Nov.) 1956.

Foltz and Ward report 10 cases of subarachnoid hemorrhage secondary to operative trauma, ruptured intracranial aneurysm, and head trauma which were followed by signs and symptoms of communicating hydrocephalus. In eight cases the causative lesion was identified and noted to be on the ventral surface of the brain. The subarachnoid block in each instance was found in the basal cisterns or within their vicinity. The time after hemorrhage before the communicating hydrocephalus was recognized or produced symptoms varied from 2 to 12 weeks, depending upon the severity of the subarachnoid block, progressive symptoms being noted in extensive lesions.

Headache was the commonest clinical symptom, and papilledema was not observed in any of the patients with increased intracranial pressure, although suggestive papilledema was noted in one case.

Pneumoencephalography was performed in cases showing progressive symptoms in order to demonstrate the location of the basal subarachnoid block, which is presumably produced through pial-arachnoid adhesions in the basal cisterns. Six patients were treated by external ventriculomastoidostomy, and they showed dramatic and rapid reversal of their neurological deficits, death being averted in three cases.

As a result of these observations, the authors speculate that congenital hydrocephalus may be secondary to subarachnoid bleeding with adhesive arachnoiditis of the basal leptomeninges.

MANDEL, Philadelphia.

THE CERVICAL PORTION OF THE VERTEBRAL ARTERY: A CLINICO-PATHOLOGICAL STUDY. E. C. HUTCHINSON and P. O. YATES, *Brain* 79:319, 1956.

Examination of the vertebral artery at routine necropsy is usually limited to the terminal intradural portion of the artery, since the major part of the vessel lies within the vertebral canal and examination is technically difficult. Recently the importance of internal carotid occlusion as a cause of cerebrovascular lesions has shown the effect of the collateral circulation through the vertebral system.

The authors examined 48 patients at necropsy by injecting the vertebral arteries with radio-paque material and removing the spine from the atlas to the seventh cervical vertebra with the carotid and vertebral arteries in situ.

From an anatomical standpoint, they found the left vertebral artery to be larger than the right in the majority of cases and of equal size in 8% of the cases. The variation in size encountered in the intradural portion was also found in the cervical portion.

In this series of 48 patients dying as a result of cerebrovascular lesions, atheromatous plaques were found in 19. The degree of involvement varied from a localized plaque with no stenosis to complete occlusion, in three cases. The sites varied in location and were not affected by the tortuous course around the atlas and axis. In cervical spondylosis, however, there was marked distortion of the vertebral artery at the neurocentral joint, which may have contributed to the vascular insufficiency.

The carotid arteries were involved in 15 cases by plaque formation, with complete occlusion in 3 cases. In four patients an infarction of the cerebral hemisphere was accompanied by infarction of the cerebellum, which was bilateral in three cases.

The authors conclude that atheroma in the vertebral artery may produce an infarct in the cerebellum and that the pattern produced is different in distribution from that of infarcts which occurred after occlusion of the individual cerebellar arteries, since the brain stem was not involved in the four cases of complete occlusion and they were bilateral in three instances.

MANDEL, Philadelphia.

COUGH HEADACHE. C. SYMONDS, *Brain* 79:557, 1956.

The act of coughing usually aggravates headache regardless of the cause, but this symptom occurs most frequently in association with intracranial tumors.

Symonds reports 21 cases in which a cough precipitated a headache in previously asymptomatic persons. Of the 21 patients, 18 were men and the ages varied from 37 to 77. A history of head injury was found in one case, and infections were present in five others. Nine of the cases of cough headache had complaints associated with disturbed auditory or vestibular function. Pneumoencephalography was performed in only four cases, and no intracranial lesion could be demonstrated. One case of cough headache cleared after this procedure.

The author believes that cough headache may be benign and the pain may be due to stretching of a pain-sensitive structure within the posterior fossa.

MANDEL, Philadelphia.

CEREBRAL DOMINANCE IN SINISTRALS. G. EITTLINGER, C. V. JACKSON, and O. L. ZANGWILL, *Brain* 79:569, 1956.

It has been demonstrated in recent years that the relationship between handedness and cerebral dominance is not as clearly delineated as was formerly supposed. The classical rule relating right-handedness and left cerebral dominance has not been altered, but the concept with regard to left-handedness has been completely changed, for right cerebral dominance is not the rule in left-handed lesions, for aphasias have been reported in left-handed patients with left cerebral lesions.

The authors report 10 cases of unilateral cerebral lesions in left-handed patients, in 8 of which the lesion was left-sided and in 2 right-sided. Severe aphasia was found in 5 of the 10 cases with left cerebral lesions, whereas in the two cases of right cerebral lesions the aphasia was not persistent. In addition, two of the five patients with involvement of the left parietal lobe presented bilateral dyspraxia and elements of the Gerstmann syndrome, in addition to mild aphasia. The only case of right parietal lobe involvement did not produce an apraxia.

Disorders of writing were severe in each instance and did not bear any relationship to the preferred writing hand. There were no findings of circumscribed alexia in these cases.

The authors conclude that speech is fully lateralized to the left in the majority of sinistrals and that cases presenting aphasia from exclusively left-sided lesions are more numerous than

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those liable to develop aphasia from a lesion of either hemisphere. Although bilateral cerebral representation for speech may occur, the authors believe that unilateral representation of speech, usually left but occasionally right, is the most prevalent form of cerebral organization in sinistrals.

MANDEL, Philadelphia.

DISORDERS OF LAUGHTER DUE TO BRAIN LESIONS. R. IRONSID, *Brain* 79:589, 1956.

Disordered laughter from brain damage is a clinical curiosity except in cases of pseudobulbar palsy due to cerebral vascular disease or advanced multiple sclerosis. Clinically, these cases show a bilateral Babinski sign, and autopsy reveals bilateral degeneration of the cortico-hypothalamic and corticobulbar tracts. In these conditions, involuntary spasmodic attacks, superficially resembling the motor manifestations of natural laughter, occur without any appropriate feeling. Such episodes are uncontrollable and prolonged and may change from laughter to weeping. Disordered laughter may arise when hypothalamic, as well as bulbar, mechanisms are acting involuntarily. In most cases the emotional feeling is not appropriate, but in other instances the patients experience amusement as the laughter spell develops.

Ironside reports cases of pathologic laughter occurring in pseudobulbar and bulbar syndromes, as an epileptic phenomenon, and in cases of excitement and other mental changes.

In the pseudobulbar cases areas of softening were found in the corpus striatum, midbrain, and pons. These lesions were in association with partial occlusion of the basilar or vertebral arteries secondary to arteriosclerotic changes.

In 20 cases of uncomplicated bulbar palsy with involvement of the bulbar nuclei, the phenomenon of disordered laughter was also encountered. Ironside suggests that the nuclear degeneration may have produced a secondary effect upon intact suprasegmental mechanisms.

Several cases of pathologic laughter associated with temporal-lobe seizures are reported. In these cases patients experienced the "déjà vu" phenomenon and the electroencephalograms revealed a temporal-lobe focus. Laughter may also constitute the prodrome of an attack or the attack itself.

The author feels that the "limbic lobe" through its intimate connections with the hypothalamus and olfactory pathways, together with the downward tracts from the hypothalamus to the reticular substance, forms the "final common pathway" for laughter.

MANDEL, Philadelphia.

BENIGN MYALGIC ENCEPHALOMYELITIS. J. F. GALPINE and C. BRADY, *Lancet* 1:757 (April 13) 1957.

Galpine and Brady report seven cases for which the term "benign myalgic encephalomyelitis" has been suggested. Early symptoms included mild sore throat, lassitude, drowsiness, vomiting, nuchal pain, backache, giddiness, and headache. Slight or moderate stiffness was variably found in the neck or in the back, with or without Kernig's sign, but in one case these signs were altogether absent. In another case muscle tone was diffusely increased in the paretic right arm, and in still another spasm developed in the left calf. Muscle tone in the affected limbs otherwise did not seem abnormal. Paresis was found in all the cases; it was diffuse and tended to fluctuate and shift. In several cases weakness affected two or three limbs, tending later to predominate in one; in other cases one limb alone was weak. Ability to use a limb ranged from frank immobility to slight reduction in power, detectable on careful testing against resistance and accompanied by aching, "heaviness," and undue fatigability. Fasciculation was observed in one case; the patient also complained of transient dyspnea and intermittent diplopia. In three of the cases there was difficulty in starting micturition, and one patient had incontinence of urine. Tendon reflexes were brisk and equal on the two sides. The superficial abdominal reflexes were absent. Paresthesiae, diffuse aches, and muscle tenderness occurred. One patient complained of photophobia and hyperacusis and of vague abdominal tenderness with pain on deep inspiration. Several patients complained of diminished mental grasp, which returned in convalescence. A low intermittent pyrexia usually occurred, but two of the patients were afebrile. All the patients were ambulant when discharged, after a hospital stay of from 11 days to 5 weeks.

Laboratory investigations were unrevealing. The cerebrospinal fluid examination showed no increase in cells, but in three patients the protein content was a little increased. As in all previously reported series, virus investigations were negative. Electromyography gave in the cases an abnormal pattern, with grouping of action potentials.

YASKIN, Camden, N. J.

INVOLVEMENT OF THE NERVOUS SYSTEM IN BEHCET'S SYNDROME. A. D. EVANS, C. A. PALLIS, and J. D. SPILLANE, *Lancet* 2:349 (Aug. 24) 1957.

Evans and his colleagues report the clinical features of three cases of Behcet's syndrome with involvement of the nervous system. A virus was isolated from the eye and brain of one of the two patients who died of the disease.

Behcet's syndrome is characterized by relapsing iritis and recurrent ulceration in the mouth and on the genitalia. Less common findings include thrombophlebitis, various types of rash, arthralgia with or without hydrarthrosis, and ocular disorders, such as keratitis, conjunctivitis, into the retina or the vitreous. It is noteworthy that Behcet's syndrome has hitherto been fatal only when the nervous system has been involved.

Of the patients reported, a man, aged 47, who had recurrent iritis for four years and recurrent ulceration of the genitalia, legs, and forearms developed spastic paraplegia with sudden onset and retention of urine. He had bilateral pyramidal tract signs. His abdominal reflexes were absent in the lower quadrants. All modalities of sensation were depressed below T-10. On lumbar puncture, cerebrospinal fluid was obtained only by aspiration. The fluid was turbid and clotted within four minutes, forming a gray gel. Necropsy was not performed.

The second case was that of a man, aged 44, who had had recurrent ulceration of the mouth and genitalia for 15 years. Progressive stiffness of the right arm and both legs developed. Intellectual deterioration was progressive and Parkinsonian features developed. He finally presented a spastic tetraparesis with predominant rigidity, nystagmus, and jaw clonus. Lumbar puncture showed his cerebrospinal protein to be 90 mg. per 100 cc. and he had 6 cells per cubic millimeter. At necropsy the brain and spinal cord were removed. In brief, the pathologic findings consisted of small focal softenings in both gray and white matter, largely confined to the midbrain, pons, and medulla, with occasional small areas of perivascular demyelination, and perivascular cuffing, most obvious in the brain stem. Perivascular cuffing was mainly related to veins. Nerve-cell changes were only slight. No inclusion bodies were found and no primary thrombi were seen.

The third case was that of a woman, aged 22, who had recurrent oral ulceration for seven years. She had had vulval ulceration for five years, intermittent blurring of vision and weakness of the right leg for two years, variable bilateral central scotoma, and attacks of conjunctivitis. Lumbar puncture revealed pleocytosis without clinical evidence of meningitis. The virus-neutralizing antibody titer was 1:28.

The authors conclude that there is much to be explained in relation to the pathology. There seems to be a discrepancy between the serious outcome in those patients with involvement of the nervous system and the paucity of demonstrable neuropathological findings. They believe that the prognosis changes completely in Behcet's disease in the small minority of cases in which the nervous system is affected. The condition has proved fatal in nearly half such cases.

YASKIN, Camden, N. J.

ENCEPHALOMYELOPATHY IN BEHCET'S DISEASE. W. H. McMENEY and B. J. LAWRENCE, *Lancet* 2:353 (Aug. 24) 1957.

McMenemy and Lawrence report two cases of Behcet's disease with clinical involvement of the central nervous system. They report the neuropathological findings and compare them with the changes in three previous cases in the literature. The lesions were multiple and had a distinctive pattern with a predilection for the hypothalamus and brain stem: They consisted in the main of innumerable small softenings in relation to the smaller blood vessels and were seen rather more frequently in white matter than in gray. Inflammatory reaction was seldom obvious, and myelin loss appeared to be secondary.

They raised pertinent observation that the isolation of a virus from one of their cases makes it necessary to ask how it can involve the central nervous system 15 years after the initial cutaneous symptoms. The relapsing character of the disease and the pathology might suggest that the mechanism of the brain stem is allergic in nature.

YASKIN, Camden, N. J.

HYPOTHALAMIC STUPOR DUE TO HYDATID CYST OF THE DIENCEPHALON (AKINETIC MUTISM OF CAIRNS). D. BRAGE, R. A. PEDACE, and A. G. NAPOLITANO, *Rev. neurol.* 93:730, 1955.

The report concerns a 38-year-old woman who during a recent pregnancy developed anorexia, vomiting, and subsequent weight loss. There also developed slight jaundice. The patient suddenly developed a delirious state, with excitement and hallucinations. Sedation induced sleep,

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but there followed a state of plastic rigidity, stupor, and blank staring. There was absolute mutism. The pupils did not react to light, and the patient did not respond to noxious stimulation. Encephalography revealed the third ventricle to be displaced upward and to the right. There was rarefaction of the posterior clinoid processes. Hydatid cysts were found in the lungs, liver, and spleen. In the region of the hypophysis, tuber cinereum, and hypothalamus there was a pigeon-egg-sized cyst, and the hypophysis was destroyed. The cerebral lesion was limited to these areas, and the rest of the brain was intact. The case is reported as demonstration of the syndrome that Cairns associated with epidermoid cysts of the third ventricle.

BERLIN, New York.

JUVENILE MULTIPLE SCLEROSIS. A. CHARLES and P. DESCHASSEAUX, *Rev. neurol.* 93:830, 1955.

There are reported six cases of multiple sclerosis beginning in childhood which were followed for a 10-year period. The patients ranged in age from 8½ to 11 years. Their symptoms were typical of multiple sclerosis, with diverse disturbances in function attributable to cerebellar, pyramidal, or cranial nerve lesions. The course was characterized by remissions and exacerbations and mild sequelae at the end of the period of observation.

BERLIN, New York.

COURSE OF HALLERVORDEN-SPATZ DISEASE. K. SIMMA, *Psychiat. et neurol.* 133:39 (Jan.-Feb.) 1957.

Simma reports the case of a 33-year-old patient with Hallervorden-Spatz syndrome of 20 years' duration. Clinically, the patient presented a positive family history, no optic atrophy, and sudden onset of a confusional mental state rather late in the course of the illness. The characteristic pathological changes consisted of pigmentary degeneration of the basal ganglia (especially the caudate nucleus and globus pallidus), diencephalon (including the thalamus, hypothalamus, and subthalamus), and cortex. The usual iron reaction was obtained in the involved regions.

PARSONS, Montrose, N. Y.

MANGANESE POISONING. A. SZOBOR, *Psychiat. et neurol.* 133:221 (April) 1957.

Szobor records personal observations on 94 patients with manganese poisoning; 3 cases are presented in some detail. The majority of patients had been ill for less than six months when first examined, and the severity of symptoms and pathology could not be correlated with the duration of the intoxication. The most frequent chief complaint was headache (occurring in over 25% of cases), closely followed by personality change and autonomic disturbances, such as vasomotor and sudomotor changes, tachycardia and irregularities of heart rhythm, faintness, etc. Weakness and stiffness of the extremities were less common complaints. The most frequent findings were referable to impairment of lower cranial nerve functions, such as altered pharyngeal reflexes and hypoglossal palsies. About 10% of patients exhibited static tremor. The special vulnerability of basal ganglia and portobulbar centers to manganese toxicity is cited, and the importance of treatment and prophylaxis is stressed.

PARSONS, Montrose, N. Y.

FURTHER OBSERVATIONS ON NARCOLEPSY. H. HEYCK and R. HESS, *Psychiat. et neurol.* 134:66 (July) 1957.

Heyck and Hess present observations concerning 14 additional patients with narcolepsy, bringing their series to a total of 44 cases. Among the noteworthy features of this group was a greater than 2:1 predominance of females (total series 21 and 23, respectively), a hereditary factor in 2 cases (11% of total series) and, in contrast to the 30 earlier cases, in which neither clinical nor electroencephalographic stigmata of epilepsy were noted, electroencephalographic changes, consisting of hypersynchronous bursts induced by photic stimulation in 2 of the recently studied patients. These abnormal tracings were not correlated with the narcoleptic attacks, and the patients exhibited no clinical evidence of epilepsy. An interesting case was that of a young printer who developed narcoleptic attacks two years following apparent complete recovery from tetanus associated with severe grand mal seizures (in addition to the usual risus sardonius, trismus, opisthotonus, and extensor spasms). The authors cite observations concerning nonspecific histopathologic lesions in the midbrain reticular substance in certain fatal cases of tetanus and hypothesize that such lesions may have been responsible for the narcolepsy by impairment of reticular tissue-activating mechanisms. Treatment, which is effective in

about 50% of cases, consists of combinations of amphetamine, ephedrine, methamphetamine, and, more recently, nalorphine hydrochloride.

PARSONS, Montrose, N. Y.

CEREBRAL METASTASES FROM CANCER OF THE LUNG AND THEIR TREATMENT. H. V. ARBOKOS, *Vestnik khir.* 2:33, 1955.

The possibilities of surgical treatment of cerebral metastases, especially of a variably localized single metastasis, are considered. In almost one-half of 82 patients the cerebral metastases were from primary bronchial carcinoma. It is not rare for cerebral metastases to cause clinical symptoms long before the primary growth becomes clinically apparent. The commonest sites for cerebral metastases are the frontal and occipital lobes; next comes the cerebellum, other parts rarely being affected. A single metastasis is found with equal frequency in all parts of the cerebral hemispheres, and very rarely in subcortical centers and the brain stem. Differentiation of cases with single and multiple metastases is of practical importance. Only those patients with a single cerebral metastasis from a primary lung tumor can be treated surgically. Nine such patients were operated on; two of them died, while the remaining seven were discharged in a satisfactory condition. Operation is also indicated when the primary growth has been removed. Decompression should be employed only when multiple metastases are demonstrable or when there are metastases in other organs, so that more radical treatment is out of the question.

SOKOLOVSKII, Leningrad.

THE BIOCHEMICAL DIAGNOSIS OF MULTIPLE SCLEROSIS. S. A. REMPEL, *Zhur. nevropat. i psikhiat.* 56:631, 1956.

The efficacy was tested of the intradermal test suggested in 1954 by Margulis and Shubladze for the early diagnosis of disseminated sclerosis and acute disseminated encephalomyelitis; 0.2 ml. of the vaccine was injected intradermally into the anterior surface of the forearm. Brucellosis vaccine and physiological solution were used as controls. The test was used in 163 patients; 43 had a clinically diagnosed form of disseminated sclerosis, 7 had acute disseminated encephalomyelitis, 45 had other inflammatory processes in the central and peripheral nervous systems (arachnoiditis, Sydenham's chorea, encephalitis, lumbosacral radiculitis), and 8 had other diseases of the nervous system (vascular affections, tumors, syringomyelia, etc.). Of the disseminated sclerosis patients a positive reaction was noted in 36, a dubious reaction in 3, and a negative one in 4; in 3 out of the 4 patients with a negative reaction the test was performed after a course of treatment; in 1 the performance of the test coincided with a period of remission; 3 of the patients with a dubious reaction had also had previous treatment. In all cases of acute disseminated encephalomyelitis the reaction was sharply positive. In other affections of the nervous system, only 7 out of 113 cases showed a positive reaction. The reaction with the control substances was in all cases negative. The author's findings confirm the results of others. Popova obtained 98% positive results in disseminated sclerosis, 100% in acute disseminated encephalomyelitis, and only 3% in other inflammatory diseases of the nervous system.

BABENKOVA, Moscow.

DISTURBANCES OF CUTANEOUS SENSATION IN AMYOTROPHIC LATERAL SCLEROSIS AND HEPATOLENTICULAR DEGENERATION. S. V. BABENKOVA, *Zhur. nevropat. i psikhiat.* 56:645, 1956.

Thirty cases of amyotrophic lateral sclerosis and 25 cases of hepatolenticular degeneration were investigated. Sensory disturbances, in spite of their poor definition, adequately present a picture which is definite for each of these diseases. In amyotrophic lateral sclerosis, subjective disturbances of sensation, pain, and paresthesia were seen in 21 patients. Objective disturbances of sensation of varying degree—ranging from those clinically observable to the subtler ones discoverable only by special investigation—were observed in all patients. The greatest number belonged to the distal type (23 cases); in 4 cases this was combined with the radiculosegmental type. As to the nature of the disturbances, hypesthesia and hypalgesia (24 cases) predominated. Asymmetry of the sensory disturbance and impairment of perceptual adequacy were also noted. Tactile sensation was impaired more than painful sensation. The poorly defined and diffuse character of the sensory disturbances suggests the possibility of microfoci in different parts of the sensory apparatus. Hepatolenticular degeneration was characterized (to a different degree in all the cases) by sensory disturbances on one-half of the body, the border extending to the midline. Hyperesthesia, hyperalgesia, and hyperpathia were found. In 14 patients disturbances of perception were observed. Adaptation to painful

ABSTRACTS FROM CURRENT LITERATURE

stimuli was slowed down; during the investigation hyperpathia appeared. Investigation of the character of the adaptation to tactile and painful stimuli points to complex disturbances of corticosubcortical interrelationships in the system of the cutaneous analyzer in both diseases under investigation. In amyotrophic lateral sclerosis there takes place a "block of impulses" at the lower levels, as a result of which weakness of the excitatory process and dominance of the inhibitory cortical process appear, which are also expressed in the increased rapidity of adaptation. In hepatolenticular degeneration a pathological inertness of the excitatory process in the cortex is present, expressed in the slowing down of adaptation. The data obtained are an argument against the concept of amyotrophic lateral sclerosis and hepatolenticular degeneration as being strictly systemic heredodegenerative diseases.

BABENKOVA, MOSCOW.

Books

BOOK REVIEWS

Auge und Zwischenhirn. By Dr. R. Thiel. Price, not given. Ferdinand Enke, Hasenbergsteige 3, (14a) Stuttgart, 1955.

The first chapters of this book relate to discrete and inadequately understood functions of the eye itself, such as the investigations of autonomic activity of the retina. Processes of the cells concerned with this activity are thought to by-pass the lateral geniculate body and proceed by poorly recognized pathways to the hypothalamus and midbrain, there relating the visual system with trigeminal, sympathetic, and parasympathetic systems. Some of the expressions of these oculodiencephalic relationships as they influence intraocular pressure are considered in the final chapter. Experimental studies utilizing light stimuli, drugs, and other factors result in changes in intraocular pressure, and the authors regard primary glaucoma as a manifestation of disturbance in the midbrain-hypothalamic relationships involved in the maintenance of appropriate levels of intraocular tension.

THOMAS PARSONS, M.D.



SECTION ON PSYCHIATRY

Psychiatric Problems of a Rapidly Growing Suburb

RICHARD E. GORDON, M.D., and KATHERINE K. GORDON, R.N., Englewood, N. J.

We have recently reported a study of the social-psychiatric aspects of pregnancy and childbearing.⁶ We noted a high incidence of socioeconomic mobility, suburban migration, and religious intermarriage in the social histories of our patient groups—both psychiatric maternity patients and a comparable group of psychiatric nonmaternity women patients of childbearing age—as compared with a control group of nonpsychiatric maternity patients. This led us to question whether generally there was a higher incidence of emotional disorders in young married people, and maternity patients in particular, associated with life in fast-growing suburban Bergen County, New Jersey.

There has been a revival of interest recently in social-psychiatric problems, since the classic studies of Landis and Page,¹⁰ Pollock,¹⁶ Hyde,^{7,8} Kardiner,⁹ and others. Opler,¹⁴ Seward,²⁰ Redlich,¹⁷ Rennie,¹⁸ Faris,⁴ and their associates have reported on the relation between emotional disorders and social class, socioeconomic mobility, rural and urban living, and ethnic background.²¹ Malzberg¹¹ and Ödegaard¹³ have investigated the influence of international and interstate migration upon emotional dis-

order. Others have noted the relation of intermarriage, marital discord, and divorce.¹
¹⁵ In several studies the problems and tensions of suburban living have been investigated.^{12,19}

Bergen County's rapid recent growth, heterogeneous population, and relatively poor social integration might be associated with social strains in certain patient groups more than in others. To explore this, we examined case records of psychiatric office patients in Bergen County and in two other counties, Cattaraugus County and Ulster County, in New York. Both the latter are rural, but Ulster has enjoyed a recent increase in industrial development, mobility, and migration, not nearly so great as that of Bergen but greater than that of Cattaraugus.

Procedure

We performed two interdependent studies. First, we analyzed the case records of Bergen County private office psychiatric patients for data regarding ethnic origin, intermarriage, socioeconomic status and change, and suburban migration. We obtained similar data from a normal, control group.

In the second study, we compared the proportions of the Bergen County patients in each age, sex, and marital category with the two groups of psychiatric patients from relatively stable rural Cattaraugus County and from moderately unstable rural Ulster County.

We have obtained objective personal data from 781 adult private psychiatric patients who sought office help in the last four years in Bergen County. We classified these according to religion of parents, national origin of grandparents, length of residence in Bergen County, and occupation of husband and

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Drs. Paul Eiserer, Jack Elinson, Abraham Jacobs, Otto Klineberg, Carney Landis, and Adella Youtz made helpful comments, criticisms, and suggestions; and Dr. Werner M. Cohn, of Kingston, N. Y., and Dr. Ian D. McLaren, of the Cattaraugus County Department of Health, permitted us to study their case records and assisted us in the project.

TABLE 1.—Comparative Incidence, in Percentages, of Emotional Disorders in High-Mobility Bergen County, Moderate-Mobility Rural Ulster County, and Low-Mobility Rural Cattaraugus County*

Office Practice Psychiatric Patients	Age	Bergen County		Ulster County		Cattaraugus County	
		Women	Men	Women	Men	Women	Men
Married maternity	44 and less	9%		4%		2%	
Married nonmaternity	44 and less	27%		30%		29%	
	45-59	10%	22%	11%	19%	10%	18%
	60 and more	3%	7%	2%	5%	6%	6%
Single	44 and less	9%	2%	6%	7%	13%	2%
	45-59	1%	9%	1%	2%	1%	10%
	60 and more	0%	0%	3%	0%	2%	1%
Number of patients			746		264		239
Percentage of women of all ages		59		66		63	

* We can see that in all areas there are more women with emotional disorders than men, but with the greater difference in rural areas. Mobile Bergen County has the highest incidence of emotional disorders of childbearing women; rural Cattaraugus has the lowest. Rural living is associated with greater percentages of older patients. Single women accounted for a larger percentage of patients in low-mobility rural county, Cattaraugus. In general, in the country, single women were relatively more frequently patients.

parents. We compared occupation of husband and parents to obtain the measure of socioeconomic status, using Hollingsheads' Index of Social Position,¹⁷ with slight modifications. A description of our scale follows.

Level I: Upper Class: Comprises families of wealth, education, and top-rank social prestige

Level II: Upper Middle Class: Consists of families in which the adults for the most part hold college or advanced degrees and are in professional or high-level managerial positions.

Level III: (a) Middle Middle Class: Includes major salesmen, subexecutives, semiprofessionals, proprietors, and the bulk of small-business people.

(b) Lower Middle Class: Includes white-collar and office employees, lesser salesmen, police, and skilled workers. This group consists predominantly of high school graduates.

Level IV: Upper Laboring Class: Consists largely of semiskilled workers and laborers, with an educational index below the secondary level.

Level V: Lower Laboring Class: Includes unskilled and semiskilled workers who have an elementary education or less, and who live in the poorest areas of the community.

We used the patients' childhood religion, not that to which he may later have been converted. Five years' residence in Bergen County was our dividing line between recent and earlier migration. We grouped our patients into seven categories according to sex, age, and marital status. These are shown in Table 1.

Our control group included 118 new mothers who were private obstetrical patients at the Engle-

wood Hospital. We obtained personal data about them and their husbands by interview and questionnaire. We have not presented the figures, but the normal group is quite comparable socioeconomically and ethnically with the young married psychiatric patients whom we are studying. We examined the records of 239 adult patients seen at the Mental Health Clinic of Cattaraugus County (the only psychiatric facility in the county) and 264 adults seen by a psychiatrist, Dr. Werner Cohn, in private practice in Ulster County during the same period of time. We grouped these patients according to sex, age, and marital status in the same fashion as described above.

We obtained information from the 1950 Census* as to the total population, growth rate, migration rate, and percentage of single and married persons. We compared percentages of patients in each category for each county.

Results

We shall first examine the results of our intensive study of private psychiatric office patients from very mobile suburban Bergen County. Later we shall compare the data from Bergen County with those for low-mobility rural Cattaraugus County and moderately mobile rural Ulster County. We have shown in parentheses the probabilities for chance occurrence calculated by χ^2 .

Bergen County.—Suburban Migration: Table 2 shows that over half the women whose emotional disorders were associated with childbearing had recently migrated to the suburbs, a much higher percentage than that for the controls or for young married men ($P < 0.01$). In general, women had

PSYCHIATRIC PROBLEMS OF RAPIDLY GROWING SUBURB

TABLE 2.—Suburban Migration *

	Women		Men	
	No.	Per-centage	No.	Per-centage
Psychiatric patients				
Married maternity	49	51		
Married nonmaternity	106	38	88	25
Single	76	20	75	2
Normal controls	118	39		

* We have presented percentages of patients and controls (aged 18 to 44) in each group who have come to Bergen County in the past five years. Recent migration to the suburbs apparently is strongly associated with emotional disorders in childbearing. In general, adult female patients of all ages show more recent migration than male patients of the same age.

higher percentages than men in every group ($P < 0.02$).

Socioeconomic Mobility: As a group the patients were more mobile both upward and downward socioeconomically than were the normal controls. This was particularly true for the childbearing group ($P < 0.01$) and for young married men and women ($P < 0.02$). The tendency to upward socioeconomic mobility is associated highly with both suburban migration and intermarriage (Table 3). Socioeconomic downward movement was greatest in single men, and was also high among couples with marital conflicts and the separated, widowed, and divorced.

Intermarriage: More of the young married women patients, in both the childbearing and the nonmaternity group, were married to persons of different religious faith (Table 4). More parents of young single women than of men had intermarried. The lives of women patients in general involved more interfaith marriage than in the case of men patients ($P < 0.05$).

Summary.—On the whole, then, the results of the first part of this study show that mobility (geographic, socioeconomic, and cultural) is highly associated with emotional disorder in private psychiatric office patients. Childbearing women, young married women in general, and women patients on the whole show more mobility than corresponding groups of men patients and controls. Now we shall look at the results of the next part of the study—a comparison of a relatively stable nonmobile rural county (Cattaraugus),

TABLE 3.—Socioeconomic Mobility *

	Women		Men	
	No.	Per-centage	No.	Per-centage
Psychiatric patients				
Married maternity	49	51		
Married nonmaternity	118	51	88	49
Normal controls	118	33		

* Over 50% of our young married patients were either rising or falling socioeconomically, with the great majority rising. This is much greater than the rate for the controls.

the somewhat mobile rural county (Ulster County), and the highly mobile suburb (Bergen County).

Nonmobile Rural Cattaraugus County.—The data in Table 1 support the findings of the previous part of the study. There is a higher percentage of emotional disorder in childbearing women in suburban Bergen County ($P < 0.001$) than in Cattaraugus County. Young married women in mobile Bergen County account for a higher percentage of patients ($P < 0.05$) (1950 census data showed there were comparable percentages of young married couples in all three counties, with Cattaraugus slightly higher and with a slightly higher birth rate). Young married people in general, men and women, account for a much higher percentage of the office patients in Bergen County ($P < 0.01$) than in Cattaraugus County. On the other hand, quiet rural living is associated with greater numbers of emotional disorders in single women than in single men ($P < 0.02$).

Somewhat Mobile Rural Ulster County.—Ulster County is a rural county with a

TABLE 4.—Religious Intermarriage *

	Women		Men	
	No.	Per-centage	No.	Per-centage
Psychiatric patients				
Married maternity	48	35		
Married nonmaternity aged 18-44	105	34	70	22
Married nonmaternity aged 45-59	28	27	30	19
Single	43	15	35	8
Normal controls	118	24		

* In this Table we present percentages of patients' marriages to persons of different faiths for several married groups of men and women and percentages of parents' interfaith marriages for single patients. There is more interfaith marriage in the lives of women patients generally than in the lives of men patients, both single and married.

slightly older population than in either Bergen and Cattaraugus. It has undergone some industrial expansion since World War II, particularly in the two years in which this patient sample was collected, with a consequent influx of new residents (1950 census rates had already shown a differential migration rate—5% for Ulster, as compared with 7% for Bergen and 4% for Cattaraugus).

In this moderately mobile county there was a higher percentage of childbearing disorders in women than in Cattaraugus County, but a lower percentage than in Bergen County. The percentage of young married women was also intermediate.

General Considerations

Rapid growth in the population of a community is often associated with a lag in the development of community organizations to care for the needs of the newcomers. Social clubs, religious organizations, and other community services are strained to provide assistance and outlets for the marginally adjusted. Apparently the strains of geographic, socioeconomic, and cultural mobility are associated particularly with the emotional disorders of childbearing women,⁵ but also with those of young married women generally as compared with men, and more than in any other age, sex, or marital group. The socioeconomic pressures upon the husband render him less able to provide emotional support to his wife, particularly during the stressful time of pregnancy and childbearing. The couples often have moved away from the homes of their childhood and are breaking up close ties with their families. Such behavior may indicate success to the husband, and often also to the wife. But in susceptible persons it creates stress to the extent that they suffer an emotional disorder and need a psychiatrist. The wife usually becomes the patient.

We can speculate as to the interrelation between sociocultural problems of suburban living and psychodynamic, physiologic, and constitutional factors. Given certain pre-

disposing factors, both hereditary and environmental, patients can withstand varying amounts of present-day stresses and strains. In a previous paper we showed that young married women psychiatric patients in Bergen County had a high incidence in their social histories of an alcoholic parent, or a home broken by separation, death or divorce, or an emotional disorder in a parent.⁶ These experiences would seem to predispose certain susceptible persons to later difficulties. Many of these persons function on the margin of adjustment. Perhaps they would not need psychiatric help if the strains of suburban living did not become overburdening. But their stressful background often is associated with the development of unstable personal psychodynamics. They are prone to involve themselves in new, present-day strains. These may provide the final push in disturbing a marginal emotional adjustment. Persons with an unfortunate childhood may try to become too independent too fast, to break with social convention and marry out of their ethnic group, to move away from family and friends to the suburbs, to try to rise socioeconomically at too fast a pace. Thus emotionally insecure persons tend to perpetuate their emotional insecurity.

Patients are often responding to authoritarian parental upbringing, and in many instances discrimination against minorities, by seeking premature independence, freedom, and economic power. They tend to defy the cultural conventions of their parents by marrying out of their ethnic group and faith. They leave the home and community of their parents and deny their need and dependence upon the support of family and friends during the trying periods of establishing a new home, childbearing, raising a family, making friends, and becoming integrated in new institutions and organizations and a different way of life. They seek financial supremacy and try to get ahead economically as fast as possible, as a means of becoming secure and independent. Perhaps this is even more of a problem with

married women than with men because of their changing role in American culture. Even faster than men, they are gaining freedom and independence, and opportunity for self-expression outside the traditional feminine position in the family.² But if the pace of the change is too fast, strains may occur. We note that, in state hospital admissions, men often exceed women in the rate of new admissions. However, in office practice, particularly in urban and mobile suburban areas, we observe more married women. We wonder whether women are not undergoing greater conflicts in their self-estimation associated with their changing status. This is less of a problem to the single women, from whom the young schizophrenia population in mental hospitals is largely drawn. But with marriage, and particularly maternity, the conflicts are brought to the surface.

Of course, this behavior mimics American cultural tradition. But it is a caricature of the more carefully planned socioeconomic rising and independence of normal American families. Many neurotics rush breathlessly and thoughtlessly ahead to a premature and unrealistic independence, to escape from the painful experience of unhappy childhood dependency. Unfortunately, they often provoke new painful experiences in their present lives and environment. Past and present difficulties together produce psychiatric disorders in the constitutionally susceptible.

We recognize that criticism can justifiably fall on this study. We cannot draw any far-reaching conclusions, for many reasons. Differences in age, marital state, and sex ratios of patients in a psychiatrist's office practice may as well be a function of the doctor's interests, personality, experience, and talents of the community in which he practices. A physician of Catholic or Jewish faith may attract a different group of patients than a Protestant. Only a sampling of the patients of many psychiatrists will answer this question. We hope to do this, and also to study the case records

of patients entering psychiatric hospitals and clinics from the county.

In Bergen County many patients seek medical and psychiatric help in New York City. Probably this is true of men more than women, and of single working persons more than of married housewives. This factor, too, will distort data. But if later studies support our present findings, a suburban community mental health program should consider primarily the housewife, and most particularly at the time of childbearing. Preventive programs may well guard against too rapid social advancement and assumption of responsibility, as well as encourage programs for a better social integration of newcomers into the community.

Summary

We have reported a two-part study of emotional disorders found in suburban private practice. In the first we made an intensive investigation of the relationships between emotional disorder and suburban migration, cultural intermarriage, and socioeconomic mobility in Bergen County patients. In the second we compared the incidence of emotional disorders in very mobile suburban Bergen County with that for rural, relatively nonmobile Cattaraugus County, New York, and moderately mobile rural Ulster County, New York. We hypothesized that suburban living is associated with greater percentages of emotional disorders of childbearing women and that this is related to the greater social strains and mobility of the suburbs.

Our subjects were 781 adult private psychiatric office patients from Bergen County, each of whom we personally examined; 257 adult private psychiatric office patients from Ulster County, and 239 adult psychiatric office patients from the Mental Health Clinic of the Cattaraugus County Department of Health. In the last two groups we studied the case records but did not see the patients ourselves. Our controls included 118 maternity patients at the Englewood Hospital and data on their own and their

husband's social histories, obtained by questionnaire and interview.

We found that living in a rapidly growing, poorly integrated suburban community is associated with a higher incidence of emotional disorders, primarily in childbearing women but also in other young married women and in young married men, as compared with rural living. Percentages of suburban migration, socioeconomic mobility, and intermarriage in Bergen County were highest in these same groups of patients. We suggested that the higher incidence of disorders in these patient groups in a Bergen County office practice was related to this mobility.

Socioeconomic mobility was more frequently associated with either intermarriage and suburban migration or both in patients than in controls.

We suggest that high geographic, cultural, and economic mobility is associated psychodynamically with an attempt at denial of dependence upon parents and family and a search for premature, unrealistic independence, with undue emphasis on financial security. Persons made susceptible by constitution and unfortunate childhood environment often perpetuate and increase their emotional insecurity in this fashion to the point of emotional disorder.

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Autonomic and Adrenal Responsivity in Psychiatric Patients

Effect of Methacholine and Corticotropin

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The advent of the tranquilizers has reawakened interest in the role of the hypothalamus and diencephalic centers in behavior,¹ which the evidence adduced by clinicians and neurophysiologists over many years had linked with affective disturbances. However, more than a decade ago Alpers² reiterated Bard's conclusion³ that the expression rather than the cause of rage in animals was dependent upon diencephalic mechanisms. Nevertheless, Hoskins, in pointing to the many disturbances of homeostasis found in schizophrenia, repeated Ranson's belief that the solution to this disease might be found in the hypothalamus.⁴

In recent years Funkenstein and his co-workers⁵ reported that a prolonged hypotensive response to methacholine was linked with good outcome following electroconvulsive therapy. Gellhorn interpreted such vascular responses as indicative of the degree of central sympathetic excitability and suggested that methacholine might prove to be a sensitive indicator of such central, and especially hypothalamic, responsivity.⁶ Although we were unable to confirm the prognostic value of the test,⁸ we showed that patients with endogenous depression manifested sympathetic underreaction, as judged by the response to methacholine, and those with schizophrenia, sympathetic overreaction.⁷ Thus, it seemed that if methacholine

were to stimulate the hypothalamus in man, there might be a simultaneous activation of the pituitary-adrenal system. This would provide an objective, and perhaps differential, measure of central nervous system response. We, therefore, compared the eosinophil response and urinary excretion of free 17-hydroxycorticosteroids following methacholine and corticotropin in a group of psychiatric patients and in normal controls. In this way we hoped to compare the adrenal response to the known peripheral effect of corticotropin with this possible central one of methacholine, the blood pressure curve providing an additional index of comparison.

Material and Methods

Method.—On three separate, and usually consecutive, days injections of the following substances were given: (1) 10 mg. of methacholine chloride U. S. P. (Mechoyl chloride*) intramuscularly; (2) 15 units of corticotropin† intravenously, and (3) 1 cc. of saline intravenously.

The order of injection was randomized. All subjects were tested in the morning after overnight fasting. The overnight urine was discarded, and all urine from then on until the injection, usually a period of not less than two hours, was saved, including the specimen voided immediately before the injection. After the injection all urine was again saved for four hours, the subjects voiding at the end of this time. A normal lunch was allowed, coffee and tea being avoided.

Eosinophil counts were done before and four hours after the corticotropin or methacholine injection.

The blood pressure was recorded at minute intervals for 25 minutes after the methacholine

* Supplied by Dr. J. H. Laurie, of Merck & Co., Ltd., Montreal.

† Acton X, supplied by Mr. Kell Antoft, of Nordic Biochemicals, Ltd., Montreal.

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injection; this technique has been previously described.⁹

Estimation of Urinary Corticoids.—The free 17-hydroxycorticosteroids in the urine were measured by an adaptation of the method of Silber and Porter.¹⁰ Ten milliliters of filtered urine was extracted with 15 ml. of chloroform in a glass-stoppered test tube (50 ml. capacity). After centrifugation, the urine layer was discarded by suction. The chloroform extract was then washed with 2 ml. of 0.1 N NaOH solution. After a second centrifugation, two 5 ml. aliquots of the chloroform extract were transferred, by means of a syringe and a long needle, to two glass-stoppered centrifuge tubes (15 ml. capacity). To one was added 0.5 ml. of the "blank" sulfuric acid reagent, and to the other, 0.5 ml. of the phenylhydrazine reagent. After shaking the tubes and centrifuging, the chloroform layer was aspirated off. The stoppered tubes were kept overnight in the dark. In the morning the absorption at 410 m μ was determined in a microcell in the Beckman spectrophotometer.

Subjects.—Five groups were tested.

1. Controls: This group was composed of nine normal volunteers, all male medical students, with a mean age of 24.4 years and an age range of 22 to 29 years.

2. Schizophrenics: This group was composed of 10 patients, all of whom had had overt symptoms for less than one year; it comprised 8 male and 2 female patients, with a mean age of 27.8 years and an age range of 16 to 48 years.

3. Psychoneurotics: This group was composed of 16 patients with mixed psychoneurotic symptoms, embracing phobic, obsessional, and hysterical symptoms, with frequently accompanying, although secondary, anxiety or depression. There were 11 women and 5 men, with a mean age of 32.6 years and an age range of 23 to 45 years.

TABLE 1.—Mean Resting Rates of Urinary Excretion of 17-Hydroxycorticosteroids on Three Days

Subjects	Rates, μ g./Hr.	Difference from Controls	t-Value	P
Controls	26.8			
Psychoneurotics	16.1	-10.7	3.79	<0.001
Schizophrenics	17.4	-9.4	2.46	<0.05
Anxiety states	15.9	-10.9	3.6	<0.01

4. Patients with Anxiety States: This group was composed of nine patients with predominating anxiety. It comprised five women and four men, with a mean age of 38.2 years and an age range of 22 to 48 years.

5. Patients with Depression: This group was composed of nine patients with overt but nonpsychotic depression, with a mean age of 45 years and an age range of 33 to 51 years.

In the last two groups an occasional control or corticotropin injection was omitted in the interests of clinical expediency.

Results

An anomalous finding was the raised resting level of urinary corticosteroids in the control group of normals. This was significantly greater than in any of the patient groups (Table 1).

The changes induced by methacholine were small (Table 2). There were no significant differential responses between or within groups, with the exception of a lowered excretion of 26.5% in the nine patients with anxiety ($P=0.05$) (Table 2).

No depression of eosinophils occurred, in contrast to the regular 60% to 80% reduction following 15 units of corticotropin.

TABLE 2.—Mean Urinary Excretion Rates of Free 17-Hydroxycorticosteroids Under Resting Conditions and Following Corticotropin, Methacholine, and Placebo, with Mean Percentage Differences

Subjects	No.	Placebo			Methacholine			Corticotropin		
		Pre *	Post *	Per Cent Change†	Pre *	Post *	Per Cent Change†	Pre *	Post *	Per Cent Change†
Controls	9	25.4 \pm 7.1	27.5 \pm 12.4	+5	23.3 \pm 15.7	18.8 \pm 6.3	-15	30.9 \pm 6.2	91.1 \pm 34.9	+210 ‡
Psychoneurotics	16	15.8 \pm 9.3	24.0 \pm 12.1	+79 §	16.6 \pm 9.8	19.0 \pm 9.7	+39	19.4 \pm 15.9	117.9 \pm 73.3	+583 ‡
Anxiety states	9	16.9 \pm 7.2	17.5 \pm 9.5	+24	17.1 \pm 8.4	12.7 \pm 9.1	-26	16.0 \pm 10.4	95.0 \pm 44.0	+580 ‡
Depression patients	9	18.2 \pm 12.5	25.2 \pm 13.3	+60	37.0 \pm 59.4	33.1 \pm 50.8	+24	--	--	--
Schizophrenics	10	24.7 \pm 13.7	19.4 \pm 24.6	-7	21.9 \pm 38.3	16.2 \pm 9.4	-22	23.2 \pm 13.6	71.4 \pm 49.0	+215 ‡

* Mean rate expressed in micrograms per hour \pm standard deviation.

† Mean of the individual differences between pre and post rates, each expressed as a percentage of the pre rate. Because of the wide range of values, such percentage differences are not necessarily the same as the differences between mean absolute pre and post rates.

‡ $P=0.001$.

§ $P=0.01$.

|| $P=0.05$.

AUTONOMIC AND ADRENAL RESPONSITIVITY

TABLE 3.—*Differential Mean Increase of Rate of Urinary Excretion of 17-Hydroxycorticosteroids Following Corticotropin*

Subjects	No.	Mean Increase, μg/Hr.	Difference from Controls	Difference from Psychoneurotics	t	P
Controls	9	60				
Psychoneurotics	16	99.6	39.6	--	2.1	<0.05
Schizophrenics	10	48.1	11.9	--	0.75	>0.05
				51.5	2.75	<0.02

In all subjects methacholine induced hypotension, but there was no significant correlation between the fall, compensatory rise, or maximum fluctuation of blood pressure and the corticosteroid excretion following either this drug or corticotropin.

Corticotropin induced a considerable increase of hydroxycorticosteroid excretion in all subjects, but this was relatively much greater among the psychoneurotics (+583%) than the normals (+210%) or the schizophrenics (+215%) (Table 2). However, statistically, this rise was highly significant for all groups ($P < 0.001$). Part of the large percentage rise in the psychoneurotics was contributed to by the lower-than-normal resting level of this group (Tables 1 and 2). Nevertheless, the absolute rise was still significantly greater than the other groups (Table 3). There was no significant difference in either the relative or the absolute rise between the schizophrenics and the normals.

Comment

It seemed clear from our findings that methacholine did not produce adrenal activation and thus, judged by this criterion, did not serve as an indicator of central responsiveness at the hypothalamic or other higher level.

The depression of hydroxycorticosteroid excretion following the drug in anxious patients was an interesting observation. The resting levels were not raised, and it was not due to change of urinary volume. No good explanation for this phenomenon exists. The work of Persky, Grinker, and associates⁹ suggested that the adrenal cortex of anxious persons was hyperfunctional, but the mechanism of such a change remains obscure. Acute stress was shown by Bliss

et al.¹⁰ to give elevated, but still physiological, levels of plasma 17-hydroxycorticosteroids. They rejected epinephrine as an activator, pointing to its failure, even in large doses, to produce adrenocortical stimulation. Emotional factors, acting through the hypothalamus and pituitary, also remained, in their estimation, merely an attractive hypothesis. They concluded that the simplest explanation was that of Sayers,¹¹ namely, that under conditions of stress the metabolic needs of the organism rose and were met by a rise in the concentration of the blood steroids. Certainly, methacholine temporarily alters the sympathetic-parasympathetic balance, but it seems doubtful if such a transitory disturbance could appreciably alter metabolic needs. Moreover, Elmadjian¹² has shown that there is no coincidental rise of epinephrine excretion following the drug. Were there, on the contrary, to be a drop of circulating epinephrine, there might be a reduction of metabolic needs, but this seems unlikely. Confirmation and extension of these observations are thus required.

The raised resting levels of hydroxycorticosteroid excretion found in the normal control group were probably due to the experimental design, which necessitated a special journey to the hospital for testing. The subjects were unfamiliar with the procedures and relatively unacquainted with the hospital setting. By contrast, the patient groups were all inpatients who had become accustomed, in varying degrees, to the environment. They had received other tests as part of their hospital investigation, which had served to reassure them and allay their fears. On the other hand, the control group, although not specifically rated, showed variable degrees of anxiety, which was of sufficient severity in two to lead them to

discontinue the experiment. However, they were a control group in the sense that none of them had overt psychiatric symptoms and all were coping satisfactorily with their studies.

The overresponsivity to corticotropin of the psychoneurotic group has been independently found by Persky in anxiety states.¹³ The most likely explanation would seem to be that the chronically hyperfunctioning adrenal increases in size and takes up a greater proportion of corticotropin, with consequent overproduction of corticosteroids. However, in all probability, there is also a stimulus of endogenous corticotropin through whatever mechanism operates, as indicated by the significant increase of corticosteroids following the placebo injection¹⁴ (Table 2).

We wish to emphasize that, for ease in performing the many determinations, only the free hydroxycorticosteroids were measured in this study. These represent merely a small fraction of the total adrenocortical steroid in the urine, the bulk of which is excreted in a conjugated form. Under usual conditions, the rise and fall of both the conjugated and the free fractions should occur in parallel. Only in cases of liver and/or renal malfunction would a serious deviation occur. Nevertheless, the use of these observations as an index of adrenocortical function is limited by the uncertainty that this free fraction is representative of the whole. Thus, the possibility exists of a disturbed ratio of free total corticosteroids as a partial explanation of the excretion of unusual amounts of the free fraction. However, Persky et al.⁹ used a method which measured the total hydroxycorticosteroid excretion and obtained essentially similar results. This strengthened the validity of our interpretation of the data obtained by the method used in this paper. Moreover, further work by Persky¹⁵ suggested that anxious subjects did, in fact, produce hydrocortisone at a much faster rate than normal ones.

An interesting subsidiary finding in this study was the normal adrenal responsivity

of the patients with schizophrenia. This was in accord with the earlier work of Hoagland¹⁶ and Bliss¹⁷ on chronic subjects. It would seem that if one judges adrenal function by the direct measures of steroid levels in either blood or urine, rather than by the indirect measures of catabolism, there is little evidence for adrenal malfunction in this disease.

Summary

Hydroxycorticosteroid excretion and blood eosinophil levels following injections of methacholine and corticotropin in a group of control volunteers and psychiatric patients are compared.

The normal controls show significantly raised levels of steroid excretion. The stress of their special journey to hospital and their relative unfamiliarity with the setting probably account for this anomalous finding.

Methacholine induces small changes only, but a definite lowering of steroid output (-26.5%), in anxious subjects. The significance of this is obscure. Eosinophil counts are unchanged. There is no evidence for adrenal activation following the drug, and thus, judging by this criterion, methacholine does not serve as an indicator of central responsivity at the hypothalamic or other higher level.

The psychoneurotic patients show a marked overreaction to corticotropin, in comparison with the other groups, and this is probably due to increased size of the chronically hyperfunctioning adrenal.

The schizophrenics give a normal, although widened, response to corticotropin, showing no apparent adrenal malfunction.

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Patient and Therapist Observations on the Circumstances of a Schizophrenic Episode

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"Now see that noble and most sovereign reason,
Like sweet bells jangled, out of tune and harsh."
—Hamlet

Bateson, Jackson, Haley, and Weakland¹ have recently outlined a theory of schizophrenia in rather general terms. This paper consists of the verbatim transcript of the major portion of a psychotherapeutic interview with a schizophrenic patient, with accompanying analytic comments based on the concepts presented in the earlier article. Thus their theory is here shown in relation with basic psychiatric data, the actual interpersonal communication of a patient, including the messages of the other party, which heretofore have too often been neglected.

This particular interview is focused on the circumstances of the patient's psychotic break (his second). Apart from acute psychotic states during military service, there has been a paucity of data available in the literature about the factors surrounding the onset of a schizophrenic psychosis, although this period of remarkably rapid and extensive change of behavior is of great practical and theoretical importance.

This is especially true if one includes as relevant data the examination of those others immediately playing significant roles in the patient's breakdown. These data are often neglected, or their significance is denied. For example, it was the reading of one of the

early papers on the psychotherapy of schizophrenia by Laforgue² that led one of us (D. D. J.) to become interested in the concept of family homeostasis.³ Laforgue mentioned that at a significant point in his female patient's therapy her sister (with whom she lived) became severely depressed. He attributed the sister's difficulty to a manifestation of the same unfortunate genetic structure that had caused his patient's schizophrenia. He did not note that the sister's depression was coincident with a sudden improvement in his patient.

Obviously, if schizophrenia is prejudged a hereditary disorder, the therapist's view of the data available to him, including precipitating factors, will be limited. Such a bias may be present when it is reported that an examination of the circumstances surrounding the onset of a schizophrenic psychosis demonstrates that there were no stressful factors operating and thus the disorder must have been physiologically (constitutionally) caused.⁴ It is our opinion that stress is a private matter and cannot be evaluated from a so-called normogenic viewpoint. That is to say, we hold that what is stressful to any individual depends on its meaning or significance in relation to his life history. It is well known, for example, that a success of some kind can play a crucial role in the onset of some depressions and in suicides, and is responsible for the onset of acute anxiety states in some neurotics. Particularly in the obscure matter of the precipitation of psychosis, we have a situation for empirical inquiry, not for a priori judgments from oversimplified assumptions. This need not mean that each case is unique and isolated; uniformities may be found

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at the level of personal significance. It is well to recall that even in the area of clearly organic disease what seems "enough stress" depends on prior life experience, and, even more, upon the state of medical knowledge. Thus, microscopic organisms were once considered an insufficient etiological explanation of organic disease, whereas the notion of "bad humors" and "vapors" was widely accepted as sufficient, though these could not be observed at all.*

Theoretical Viewpoint on Family Interaction

Bateson, Jackson, Haley, and Weakland¹ postulated that part of the etiology of schizophrenia is a communication sequence they labeled "a double bind." A double-bind relationship, most simply, can be described as a hostile dependent involvement where one of the parties insists on a response to multiple orders of messages which are mutually contradictory, and the other (the schizophrenic patient-to-be) cannot comment on these contradictions or escape from the situation. Obviously, a double-bind relationship can exist only within a special family or group relationship, since, for example, a child could break out of a double-bind situation with his mother if his father were capable of handling such contradictory multi-leveled messages and thus setting an example and offering support to the child.

For purposes of description, we speak of the child's being in a double-bind relationship with the mother, and yet the mother is as much a victim caught up in a morass of her own maneuvers as the child is. In a real sense, she needs the child for her own mental economy. Evidence for this viewpoint can be found in observing what happens to the family interrelations when a schizophrenic patient makes a successful recovery while living within the family framework.³ Similarly, the siblings or spouse of the patient can be one factor in the double-bind situation and yet to the

casual clinical observer may appear as the healthy one. The person who has culturally sanctioned motives and attitudes will have obvious advantages over the other partner. Such a person may be severely crippled, for example, by inflexible righteousness and morality, and yet never come near the confines of a psychiatrist's office. This whole question of "Who the kept and who the keeper?" which is central in the interview and discussion to follow, is a complex and important matter, which needs further study.

The Patient and His Family Situation

X. is in his middle 30's. He was born, one of several brothers, in Eastern Europe and was brought to the United States as a young child. His father died when he was an infant, and he was raised by his mother and an angry, violent stepfather, now also dead. The mother, who is a member of a reformist Orthodox sect, X. describes as inordinately prideful, stingy, and retaining her old-country ways. X. seems to have been somewhat solitary as a child, but there is no evidence he had any incapacitating difficulties, mental or physical. He completed high school successfully, and shortly afterward went into the Army. He had about two years of service in the United States and the Pacific areas as a laboratory technician. Two weeks before the end of the war, he had an especially good letter from his favorite brother, stating they should get closer together after the war. A few days later X. learned that his brother had been killed in action, and shortly after had a psychotic attack, of unstated nature. He was hospitalized, was returned to the United States, and three months later was discharged "in partial remission." X. now appears to minimize this episode, saying he was not so much "crazy" as afraid he'd be killed like his brother and desirous of getting home.

After discharge he entered college, taking a pre-medical curriculum. However, in three years he had completed only two years' work, and in three more years he had done one year's work. He then left school and began to work at a variety of minor technical or clerical jobs, changing every year or so and repeatedly getting into difficulties with employers and other employees.

In 1950 he married a girl whose family came from a geographical and religious background similar to his own. Her mother had died when she was a young child, and at first she was reared by her father and his sister, but later was sent by her father to a Catholic school. Catholicism and her relationship to the nuns remain very important to her. Mrs. X. has moderately severe epilepsy.

*For further discussion of this matter, see Jackson.⁵

At the time of the patient's second psychotic episode, which is discussed in the recorded interview, he and his wife and two small children lived in an apartment building owned by her suspicious, irascible, and aging father. His mother lived nearby and, despite being a source of friction between the patient and his wife, was a frequent visitor in the home, partly because she was available as a baby sitter. There were frequent arguments among the various family members over religion and finances. Finally, as described in the following interview, X. again broke down and was hospitalized, with a diagnosis of "acute schizophrenic reaction, paranoid type" and "schizo-affective psychosis."

Interview and Comments

This interview took place four months after the patient's break. He had then been seeing the therapist in three hourly interviews a week for 10 weeks. There had also been several joint interviews with the patient and his wife. All of these interviews were tape-recorded, with the knowledge of all parties. The first third of this transcribed interview, before discussion became focused on the circumstances of the break, is here excerpted and summarized to cover certain points importantly related to the later material or to our basic theory. The final two-thirds is given verbatim, with no editing except concealment of names. Our ideas and comments developed subsequently are interspersed, in parentheses:

X.: Could you help me get out of here?—I mean—within a month or so?

T.: Well, I told your ward—I don't want to do anything to hinder you getting out of here—

X.: Well, that isn't positive—I mean that's—didn't give me a push—I have to get a little help, to get out—

(X. opens by asking for specific help. This is a realistic request in that the therapist might be able to influence an administrative decision, but X. also shows his own feelings of helplessness, which appear more fully later on in the interview.)

Then X., in explanation of why the therapist should give him a push, starts to develop two themes of concern about staying in the hospital: 1. The present ward doctor, a woman, is about to leave, and whoever takes over might leave him in for months. 2.

He is uncertain about going home and asks the therapist to take a stand.

X.: . . . I'd either stay here completely or go home completely—if you gather what I mean—

T.: Why do you suppose you might have a feeling like that?

X.: . . . Well I don't know—why I might I mean it's the—as if it's the same question—in a small way it's as if why, uh, why did I have the nervous breakdown in the first place—it's just about the same question—and if I knew, I'm not saying I could do anything about it—but at least I could—at least I could—understand—what it was—

(X. states he must either stay in or get out—a black or white viewpoint. This is almost immediately related to the psychotic break as "the same question" as that of why he broke down in the first place. X. also deals with the question in terms of the "illusion of alternatives," a concept to be developed in the discussion.)

T.: Has it got something, maybe, to do with changing what you're adjusting to—back and forth? That you sort of adjust to being home and then adjust to being here—or something like that?

X.: It might be, that might be it—(pause) Well, I wonder if it really would do me good to to stay away from my mother more, like B. [his wife] seems to want—maybe it would help, uh—less, uh, it would cause less conflicts; I'm not sure of it myself; but it might, might be part, it might be true; in other words it's a—(pause)

T.: This, again, is sort of around the topic—should you stay in one place, or can you live with more than one sort of thing at a time—

X.: Well, in that case it seems as though B.—B. would be disturbed if I would see mother too much, or she more or less demands, to know every single thing we say, and then she'd notice whether it was disturbing *me* or whether it would disturb *her*—(pause)

(When the therapist essays a general statement about X.'s "this or that" problem, originally about home or hospital, X. shifts to mention a similar conflict around "wife or mother," emphasizing his keeping away from mother more as possibly being helpful, though he lives with his wife, and the

transactions immediately preceding his break mainly concern his wife. He is covertly asking how the therapist feels about his leaving or staying, and if there is a disagreement with the female administrator.)

X. then shifts back to difficulties about getting out of the hospital—could his wife help?—and especially the change of doctors; maybe the new one will think differently about him than the old one. The therapist ties these several situations, and feelings of helplessness, together, then comments:

T.: (It looks as if) you are afraid that one person will say one thing, and another person will say another thing, and you won't know what to do about it.

X.: Well, that's—that's right; in other words, all I can do is just—uh—take the general opinion—in other words, it's a— it's sort of a coming together of the minds—like—well, in one respect if I should compare—uh—coming together of the mind of my mother and B.—well, and if I compare that with, say, coming together in my mind of you and the [ward] doctor—if you and the doctor had the same opinion of each other as B. and my mother have of each other, well, they'd never be a coming of the mind together—there never would—but, thank God, there isn't *that* particular situation; there isn't an enmity between you and the doctor over me—see—

T.: Um hmn.

X.: Such as there is between my mother and B.—so, of course, I imagine there is more hope of getting out—than, uh—than that.

(X. now overtly connects the therapist and ward doctor with the mother and wife but does so by utilizing denial. It is not certain how much grounds for fearing such a conflict he had in reality, though it can be said that if one existed, it would probably have been mainly covert, therefore all the more difficult for him.⁶ There may have been a repetition of his childhood situation, as covert or tangential maternal-paternal conflict seems common in the families of schizophrenics.⁷

There is then some further discussion of X.'s feelings of helplessness, which he contrasts with opening his mouth and saying

how he feels. But if he does, his wife, for example, would get angry. She might even get a divorce.

(Why does he feel helpless? As X. sees it, it is because if he should assert himself by voicing his feelings, he might be abandoned. But the situation is actually more complex than the mere alternative of keeping quiet or speaking up. It later becomes evident that also if he keeps quiet his wife is angry and implies he is only a "mother's boy" or a "weakling," which she does not want. Thus, the apparent alternative of keeping quiet or taking a stand does not offer a real choice—the two possibilities lead to the same outcome, the threat of abandonment. The question, then, becomes one of why he cannot see and comment on the fact that whatever he does he is blamed. This situation is the center of his helplessness.)

Then X. says that sometimes he does try to get his way, and speaks of getting his wife to promise not to go out to church alone at night, because she once had an epileptic attack on the way; she told him about the fit, showed her bruises, but said, "Don't worry."

(X. mentioned his wife's "spells" very briefly and obliquely in his previous remarks about having to avoid angering her. He seems to feel caught: If he is assertive, she might have a seizure—thus abandoning him, as well as increasing her "control" by helplessness. If he is compliant, she goes out alone at night, and may have a seizure, too. He also allows himself to be trapped by the way she exhibits her epilepsy but then rejects his concern about it.

An earlier fear that his mother might be hurt by his violent stepfather, and he be helpless about it, expressed in other interviews, may underlie these current concerns. As a child, he learned there was a high value placed on his protective concern toward his mother.)

The therapist inquired about possibilities of argument or discussion between X. and his wife.

X.: Well, I'll say that these years we've been married, we've argued quite a lot—quite a bit—

T.: Uh huh—

X.: and we—I guess she'd call them discussions; I call them arguments—over religion, over finances, over things she planned to do, and I've always tried to—well to me, to take the more cautious—

T.: Uh huh—

X.: Attitude, and as far as religion, well her—her religion is all—is all right, it's just *the one* and I try to—to show that, well in a way, I didn't quite agree with that, and, uh, I don't know—she seems to like to—I know she said she's had a lot of discussions about religions, and she defended Catholicism and nobody could beat her down on it, nobody could. She took pride in that—and I found out later that—even with my utmost reasoning and; uh, whatever I could do, I never could, uh—just like she'd say, I never could beat her down; she'd never agree. It's just like, uh, she—an extreme case I was going to mention, she gave me her promise not to go to this church at night, and yet she went without telling me—and then she said, "Well, that's not deception," because it's a good thing she was doing, and you only practice deception when you're doing an evil thing. Well, of course, what can—you see there's a definition that—how can you fight a person when they set their own definition?—that isn't playing the ball.

(When he tries to discuss things, his wife defeats him by sticking to one extreme position, though one that also has strong cultural sanction.)

But if he does manage to seem in the right, despite his usual tentativeness, she shifts from one extreme to another, by redefining everything at a *higher level of interpretation*, which she controls. She deceives him about not going out to church, but because she is going to *church*, this deception isn't deception. X. is thus involved with a person who overtly gives him contradictory messages, and denies that this is so. It is our impression that preschizophrenics are particularly blind to changes of context as a controlling device by others. This difficulty in handling contradictions appears more fundamental than X.'s somewhat similar difficulty in handling opposing influences from two different persons.)

There is some more discussion of arguing. X. reemphasizes with another example that if someone shifts definitions, you not only can't win; there's no getting together. He didn't think arguing was disturbing until he had this breakdown. People take advantage of others in arguments; but if you do, they may resent it and pay you back—(From here on is verbatim unbroken sequence.)

T.: So that this sort of brings up some things we were talking about before—a couple of times you were on your way to getting your own way—and then you begin to feel sort of uneasy about it—even with B. a couple of times you were arguing with her about something, looked like she was giving in to you; you sort of then said: "Well, go do it your own way."

X.: Well, I did that a couple of times, here—yeah—only before, when I used to argue with her, I'd never do that; I—I, uh—I wouldn't give in that way. Uh—I imagine, uh, I'm getting back to where I could argue more now, but, uh—I'm thinking that the—maybe that isn't the best thing to—to argue, I know—all—the only—sort of a clue—that I have—it's, just before I had my nervous breakdown, I had an argument with my—father-in-law, and I was kind of arguing with B. in a way, although she didn't think it was much of an argument—but I got very disturbed over it—only I know this was the week where I wasn't feeling well. And I even woke up—from a dream that was very uncomfortable, I couldn't—I don't know what the dream was, just sort of an uncertainty, just that's all I can describe it, an uncertainty, and, uh, when, uh—another thing—we stayed out a little late there—it was on account of B. that I did that—I—I, that's why I'm kind of blaming her, for the occasion, and my father-in-law really raised the roof—and he seemed to despise us so much, and it hurt me; in other words, that attitude in his—it seemed to hurt me, and I could see that my mother was siding with my father-in-law—and that hurt me also—I tried to explain, but they wouldn't accept the explanation.

(X. recalls having a horrible dream the week he got sick: He can only say it was about "uncertainty." But uncertainty is a main theme of the whole interview, and he goes on at once to mention one of the situations it is related to—being caught between two other people; the other being concealed or denied contradictory messages from one person.)

And he can't resolve the uncertainty, because no matter what he tries—argument or explanation—

he is rejected. All these matters are mentioned in close connection with his psychotic break.)

T.: What was this about?

X.: Well, we went out to buy him some apples, and we—we stopped in at his apartment house and got some information for him, and B. and I went shopping, and we spent quite a lot of time in the store, and where she likes to go and—we went out to change a wrist watch for her—and it was way on the other side of the city—and then she wanted to stop in at the convent—at the, the M—High School, and she spent quite a little while there with the nun, and we were talking, and uh, fin—finally, I went home, but I phoned into the postoffice that—that I was ill, and, uh—I really wasn't too ill; I just couldn't make it on time they—they have a ruling—if you don't make it on time they—especially for subs, like me, they could just send you home, see—without working—

T.: Uh huh.

X.: That's your punishment. And so I phoned in, and, that's—that's when my father-in-law got so disturbed, because he knew I'd missed the work—see, I missed work; I said: "Well, it's not fatal; I haven't done anything wrong. They know I am not coming!" and, uh, yet he, he just seemed so upset over it; and my mother told me: "He's been upset now for about three hours, waiting for you people to come home, you know—you—you've been gone all day."

(He was doing things for his wife and her father; this made him late, and he was blamed for it. Again, it probably appears to him that if he is "good," he may be accepted; but this is illusory.)

It seems that X. is afraid to face openly even the possibility of a clear rejection—in this instance at the job—another uncertainty arising largely from an apparent "wife-or-job" alternative—and has to deal with this evasively by saying he's sick and thereby lowering his self-esteem.)

T.: What upset him so much about this?

X.: Well, because we should have returned so much sooner—according to *his* mind—and what—what it, he thought we'd gone out here to Palo Alto to B., B.'s aunt; that's what he thought, or else we took a trip

somewhere—and, uh, in other words, it just wasn't right for us to do that—that's what.

T.: I find it a little difficult to understand what he was so disturbed about, particularly since just Wednesday afternoon B. was talking about how lenient he was about her coming and going before she was married.

X.: Well, uh—that's true, but this case of her—her aunt, see—she never, she never tells when she visits the aunt—he had a misunderstanding with her—and he doesn't like B. to visit her, although now she says finally that he has agreed to that, to her visiting her aunt—but he still—he still doesn't want to have anything to do with that aunt, and, uh, I don't know—he didn't know that we went to the aunt—which, we didn't go—but he thought that we had taken a trip, and he was disturbed that—uh—

T.: It looks like he thought—you might have?

X.: Well, we might have, but that didn't seem to be the thing that was bothering him—the thing that bothered him was that I should've been to work on time; in other words, it's so important—to get to work on time and—and see—see the work is *very* important as far as he is concerned—

(X.'s difficulties again force him to be caught in the middle. The father-in-law is probably angry with his daughter for deceiving him and for irresponsibly keeping her husband away from his work. However, he takes it out on the patient, who accepts the full blame; he can neither point out the father-in-law's contradictions about an agreement that wasn't agreement (as daughter's deception wasn't deception) nor get together with him to blame her jointly for being irresponsible.)

By his accepting being the scapegoat, perhaps X. escapes, temporarily, from facing problems of contradictions, mixed feelings, and deception, with the father-in-law and with his wife.)

T.: What importance does that—does it have to him?

X.: Well, that I should have a good job, and keep the job, and not—not dillydally with it. Of course, I—I always—I know I said always—be punctual, and I always try to work good—and just—for my own, it's my own nature—and not just his—I know that—

T.: Although what it strikes me, is that he certainly seems to take a very powerful concern—

X.: Yes, it's a paternal attitude—very, very interested in and—and, uh, in a way, I—I always wanted to cultivate his good will, like I told you all along; in this case I could see that—that we just had that argument and then, this happened—you see—it just sort of added fuel on the fire—

T.: And, in this argument about you, uh—should have been there on time to go to work—your mother also got into this and—?

X.: Oh, yes, she jumped in both feet—and, "Where have you been?" and she didn't say too much to B.; but she was really digging into me there, and, uh, well, I—I just told them: "Simmer down; simmer down," you know; "Everything is all right; there's nothing to get excited about."

T.: Were you all together at this time?

X.: Yeah; she was home looking at the kids.

T.: Uh huh.

X.: When we go on a trip like this, I'd usually try to get my m—my mother to look after the children; it's one of the reasons I always like to have my mother in good terms with B. so—just for that purpose—

T.: So that really everybody—just before you had your break then, everybody was on good enough terms—so that—

X.: Oh yes—

T.: You were all gathered together—in the house.

X.: Yes, definitely—yes.

T.: So that the great d—I mean regardless of some of these previous disagreements—

X.: Yeah—

T.: Uh—

X.: Still—

T.: The real thing didn't blow up until you got sick—

X.: That's right—that's very true—yeah.

T.: I mean, this in spite of—

X.: Yes, in—

T.: In spite of what I heard about before—

X.: That's right—(overlapping)

T.: About the time B. was so upset—by hearing what your mother was saying and—

X.: Sure—that's right; in other words, this finally was enough of a—of an occasion to cause a permanent—or it looks like it's a permanent cleavage—in other words, he's—when he's getting now to the point where you'd—he calls my mother a snake—and he's so vicious against her, and B.'s threatening divorce, I want—well, you see this is, they're just playing it—pretty tough now—

(X. accepts his father-in-law's control and interprets it as benevolent, a paternal attitude, to which he responds with an effort at "goodness" again; he aims "to cultivate his good will." Yet everyone is jumping on X.; how does he himself invite this? Perhaps just by his "goodness.")

He fears that everything will fall apart and that he will be completely abandoned, left without anyone. A similar fear seems implicit in his statement that he wants his wife and mother to get along so that the children will be cared for. This fear seems extreme, but his childhood situation has given him real cause to be concerned about the solidarity of the home.

It is perhaps also relevant to this abandonment theme that his first psychotic episode occurred shortly after the news that his favorite brother had been killed.)

T.: Um hm.

X.: That's it; that's all I could say—

T.: But this—this situation when you got home then; it seems like you must have felt like everybody was jumping on you for something that wasn't even really your doing—and—

X.: Well—

T.: I mean, as you recounted it—

X.: Well, I felt—(overlapping)

T.: It was mainly B. was going from here to there, and taking a lot of time about it.

X.: I felt that way because, whenever I go with B. it takes so much, uh, time. In other words, I always—the time—try to hurry her up. "Hurry-hurry-hurry up" and, uh—seems—she isn't the hurrying type. And no doubt we, we stopped in, uh, a drive-in and had something to eat, and, uh, all I know is that B. wanted to go to this, uh—convent; and I blew up, and I said: "No,

you're not going; we're not going; we got to get home." See—I knew I had to get home; I thought I'd make it in time for work, and then, uh—I felt, then I had just this nagging—what it was—I—I know I wasn't feeling too well—and, I told her—"Well, look, you're driving me nuts." Well, I really didn't blame her—I wasn't really blaming her for it—I said: I don't feel well; I can only do one thing at a time"—I know I said—but this's actually the way I felt—

T.: Um hm.

X.: I couldn't seem to—to just be relaxed—I had to just—keep my mind on one track—and I said: "Well, if—if you'd like to go, to go to the convent, it's all right with me." So she said, "O. K."

T.: You mean you changed around—

X.: Yeah, I changed, I changed around—I know I'd done that a couple of times before, but not too often, 'cause—maybe I felt sorry for her or somethin'—I knew this was an opportunity for her to see this nun she loves so much—and, uh—she always praised her so much and everything—she's just like a mother to her, and the one person in the world in whom she has complete faith, and all that sort of rot—well to me, you know, it's—to me it's rot; maybe to her it isn't.

T.: Why didn't she take care of going to see the nun? Instead of getting you to do it for her and miss your job?

X.: Well, uh, in a way I guess she knew that I, I probably could call in, uh, late, and, uh—so that's what happened—we—

T.: And what did B. say when this argument developed when you got home?

X.: She didn't have much to say about it—she was rather kind of quiet—

T.: And she just left you to take it?

X.: Well—she went in with the children, and I think she might have said a couple of things—uh—uh, but we did not mention the fact we stopped in at the, at the convent—I don't think I mentioned it—to my father-in-law.

(When the therapist puts some of the blame on the patient's wife, X. rises to the occasion and agrees: He had told her: "You're driving me

nuts," a comment on her communications. But he soon backs down again; as the interview goes on, in general he minimizes and excuses her part in the situation, and emphasizes difficulties with her father. This relative protection of her seems related to attitudes around "mother." Mrs. X. went to the convent to see a nun who was "like a mother to her"; her leaving X. to face the music later was excused by her going in to be a mother to their children, and so on. X. also tends to minimize his own mother's part in the attack on him.

X.'s emphasis on the father-in-law and minimization of any maternal part in his difficulties are similar to the situation we have observed in other families of schizophrenics: The father is rather like one of the children, and he collaborates with them—often by engaging in manifest, but unessential, conflicts—in screening the mother's activities from view.)

T.: Why was that?

X.: Well—I don't know—he, he may have thought that wasn't exactly a good excuse—you know that—if it been a flat tire, or, something wrong with the car, well, you see, that would've been a good excuse; but just going to the convent, I don't imagine that it would have been such a good excuse, and then my mother, I know she wouldn't agree with that—

T.: Well, neither, neither one of them would have accepted this—

X.: That excuse—

T.: As any reason.

X.: Yes, and I told them—

T.: Even, even though your father-in-law was the one who put B. in charge of the Catholic nuns in the first place.

X.: Yes, that's right—and my mother had disagreed with him like that as though he had committed a crime—I know—she, she'd mentioned it to him: "Why did you do that—why did you put your daughter, and make her a Catholic," and all that, uh. As far as she is concerned, see, she showed her intolerance to the Catholic Church right there—and many other times—so finally, you see, she's—she did work herself so that—that is why I don't blame myself—*myself* for—anything that happened: I know I did open my mouth, in a few vital spots, such as to Father H., and—

(It seems that only something practical and accidental would serve to excuse his lateness—

something extraneous. Anything relevant, especially personal desires and feelings, would bring up all the old differences they seem unable really to resolve, such as that between X.'s father-in-law and wife over the convent and the aunt; X. seems very eager to avoid such conflicts.)

T.: Well, I still think about this particular time, which seems pretty important—and it looks like so you must have felt that you were sort of standing there all alone, everybody giving you hell for something that wasn't your fault—

X.: Well, uh, I just took it—

T.: Why should you take it?

X.: Well, I don't know—that's a good question—I, I don't know; it's a good—maybe I, I should have blown up and let off steam; maybe that would have helped—

T.: Why couldn't you just say: "B. insisted on going to the convent"?

X.: Well, you see—it's sort of a mixed-up affair—I, I'd say that, and then what, what would I get from B., see? You understand?

T.: Well, didn't B. insist on it?

X.: Well, no, she didn't insist on it; that's just it—she, she asked; and then I blew up and told her "no"—

T.: Yeah—

X.: And then I changed my mind and said: "Well, would you like to? All right"—see—

T.: So partly you, you went along with it—

X.: See, I went along with it—

T.: Well, then, we get back to the question: Why did you go along with it?

X.: Well, that's a good question, too; like I said, I felt sorry for her and thought, well, she, if't means so damn much to her, well let her have—uh, let her, let her have her way—I know she wanted to see her—she, mn—I had a feeling if we wouldn't go, she'd be—s . . .

T.: She'd make you suffer for it.

X.: (overlapping): She'd be pouting down her nose, yes; she'd be pouting down on her nose—

T.: O. K.; so in a way you feel she did make you go—

X.: In a way, yes—it's in other words it's ah—I—I'd the experience before, and I sort of learned that—in other words, if I—if I'd agree to her wishes—you see it'd be easier on me—she'd have a better attitude; she'd have a happier attitude. I don't know why—that affected me so much when she had the—nasty attitude, and there'd sort of be of tension on me—for a long time; maybe it would last a day or two—

(Here X. also shows again how he, too, can't settle on anything. Just as he is about to take a definite stand of his own, he backs down, again under the illusion that he can buy acceptance.)

T.: Yeah, she would sort of hold a grudge on you—

X.: Yeah, she'd hold a grudge and—

T.: Make you know it—

X.: Yeah, and I thought: "Well what the hell! See 'em and"—uh—and on the other hand, it turned out the other way—those two were waiting for me with a—might say a loaded shotgun, I mean, that is emotionally; that's what it was—they just blasted into us and, uh—well, I thought, I didn't think much of it—then, the next day, I didn't think anything untoward, I said, well—uh, I slept late, as is my custom, and, uh, went to work, and then after a couple of hours, I started to feel funny—

T.: Uh huh—

X.: I, I didn't know why I—I but—first I thought the—the supervisor was watching me—and, sure enough, I kind of thought they were watching me—so, "Well, am I doing something wrong?" and, then, I—I had the feeling that there was tension in me—and, and if I could only last out until—well, until lunch time, or last out until, uh, a couple of hours, I'd be all right, it would pass—

T.: Uh huh.

X.: Well, seems though there was just a little too much tension just to pass that lightly; so—that's all I can say—it seemed to build up more.

T.: Um hm.

X.: And, uh—I got sort of a befuddled state, where I couldn't seem to—my simple task was to separate long letters from short

letters, see? It's very simple; I mean there's nothing simpler than that, and then I started getting confused—

T.: Uh huh—

X.: I seemed to pay too much attention to the in-between letters. Couldn't decide whether they go with the long or the shorts.

(The problem of decision versus terrible uncertainty has been a theme throughout. It has appeared in relation to dealing with differences of opinion between two other people, and dealing with contradictory messages from one person. Here, as X. nears his break, it reappears in a bare, almost diagrammatic form.[†] This instance is without manifest interpersonal context; however, it can certainly be related to the patient's own tendency to be an "in-between," and his need to please and conciliate everyone, all the time, by "doing right.")

T.: Uh huh—

X.: So, well, I felt, I felt that was kind of funny: I talked a little to the guy who worked on the other side—and, then, I—I couldn't seem to give the right answers; I was—I seemed to be too critical of myself. I don't know why. I thought the best thing would be to shut up—and yet I couldn't seem to shut up—

T.: Uh huh.

X.: The best thing would be to just keep quiet; and if I could have kept quiet that would have been fine; but I—I didn't. I seemed to talk with the—uh—then I just get disturbed and wonder: "Am I saying the right thing?"—then I asked one of the guys, I said: "Well, I just don't feel right; what shall I do?" "If you don't feel right, why don't you go home?" I said: "Well that's a good thing—I mean—I don't—this would be the first time I'd have to go home in a year and a half"—and I went up and asked—and, uh, well, later George told me—he said—"Well, your face was white, just white"; so you see it really was evidently . . .

T.: Uh huh.

[†]X.'s collapse over inability to discriminate between long and short letters sounds much like Pavlov's production of experimental neurosis in dogs by setting them a circle-ellipse discrimination problem, which was eventually made too difficult by changing the ellipse nearer and nearer to circular form.⁸

X.: The autonomic system, or something, wasn't working right—the blood was drained from my face, uh; something was wrong; so, when I went home, I took a jitney, and I just kept quiet all the way, just trying to think: "Well, how could I explain this to my—father-in-law or to B. or to mother?"

T.: Uh huh—sort of like things would be back where they were the night before?

X.: Yeah, that's right—

T.: Uh huh.

X.: I thought well, well; then I started to get disturbed—sort of like in a trap or something—

T.: Like there didn't seem to be any way out—

X.: There's no way out, that's right; and when I got in, I just started crying—then when I was crying like I told you, I felt in a way: "This will punish the old bastard!" You know what I mean?

(X. is more and more concerned with "rightness"—"Am I doing right; am I talking right; am I even functioning right physically?"—but how can he find out? Desperate as he is, he feels it is also wrong to ask about it, or leave work; and if he goes home, it will be like the night before; so he's trapped.)

In our view of schizophrenia, the trap is real, and centers on the fact that the child must not bring it out if he does feel bad or upset, because this is to his mother an accusation that she is not a "good mother," and she cannot stand this. So the line of communication for possible correction of difficulties is blocked.)

T.: Uh huh.

X.: The old man. And this way, of course, I wouldn't talk with him or anything, and he—just sat around for a while, then after th—minute you see, B. managed to, take me to the—uh—hospital, but actually, you see, now that I look at it, nothing actually—st—uh—started, started me wrong—didn't happen—until I—I, in fact when I was in L. Hospital for a while, for a few hours, and they couldn't agree where to send me, or—I wanted to go home—see? I told B.: "Well, let's go home; let's take a taxi and go home, or something." "No, let's wait a while," and then when they finally decided to, to take me to M. Hospital,

I had the idea that this, uh, was one of the aides dressed up as a cab man—

T.: Uh huh.

X.: And I thought: "Well, they're just testing me out"; see, already I was imagining things—

(X. has a delusion involving deception but explains it away, much as his wife explained away her deceiving him—"It's for a good purpose.")

T.: Uh huh—

X.: And then, uh—the funny thing is that that darned meter seemed to spin fast, you know, real fast—and then it slowed down; it almost stopped just—just—when, actually you know darn well that the meter just has one constant speed.

T.: Uh huh—

X.: So then that confused me; so I says: "Well, is the meter rigged?"; you know—

T.: Uh huh.

X.: For this—and then I was getting very upset; I—I was saying: "Well, you're going the wrong way"; I'd say: "Well, B., you should go this way"; then finally, after a while: "Well, you're going the right way; looks to me like I know part of the city" and, uh, finally I mean I kept this up until the doctor at M.—M.—I don't remember the first night how I slept, but I sure got very upset for the next few days—

T.: I wonder if we go back a minute again, to the night where the argument went on—uh—what did you do—while they were—while your father-in-law and your mother were telling you this was all so terrible?

X.: Well, I know he was in no condition even to just talk to. He just s—stalked off, sullen, and I thought: "Well, I better let him cool off for a while."

T.: He just sort of gave you hell and then walked away?

X.: Yeah, and with her, I just tried to tell her, but she just, you know—mother was saying: "Well, you're wrong, you're wrong; you know you, you shouldn't have done that," uh—

T.: And you mean nobody even gave you a chance to talk back to them?

X.: That's right—I couldn't reason with her; she's, uh, all in his favor, I mean, and,

so, I didn't say much to B.; I know I was—but I don't know whether that was actually what caused it—

T.: Well, I'm just trying to get a clearer picture of the circumstances—

X.: That's what happened, though—

T.: So you didn't really say much to anybody?

X.: No—so, uh, well, it's hard to just keep, keep something in you, in—n; just keep it in you, uh, and be to blame for it—I mean—that's—

T.: Sure.

X.: Then I realized—you see, this was such a small item actually; this was a very small item. The thing that I really, I raised a fuss over, like I say, was when he accused me of not even paying the interest on the—this property—damn property, I—it's not worth over \$10,000 or \$12,000; he paid \$17,000 for it, and, uh, it is such an inconvenience after he bought it in, and then so many disadvantages—

T.: How come you—when—after they all told you you were all in the wrong about this—you didn't say anything to B. either?

X.: Well, I felt that B. knew the circumstance, and that she—she was with me all day, and—uh—(pause) I kind of felt that she sympathized with me in a way; you know what I mean? I mean, she didn't have much to say but—I knew that she wasn't against me—

T.: Was she there at all when they were giving you the devil?

X.: Yes, she was right there—

T.: Um. But she didn't speak up?

X.: Well—I don't know—uh—whether she spoke up or not; if she did, I didn't pay much attention to it.

T.: But, at any rate, you don't have any recollection of her saying anything about: "Well, I wanted to go to the convent," or anything of that sort?

X.: No; no, she didn't—I don't think she—(pause) Later, I think I told mother that we went to see this nun, and she says: "Oh, that's it"; you know—it's B.'s fault, you know—I think I told mother that—she

jumped on B., as she usual—she usually does; she usually does blame B. for everything, see? As far as mo—mother is concerned, everything is B.'s fault, and, uh—so, uh—

T.: "Later" when do you mean by "later on"? You mean that evening? or

X.: Yeah, she—that evening—yeah, I—I mentioned it to her—then again; well, it's true, one thing, mother knew a lot about our life, a lot of things—I, I'd tell her—uh—you know, in other words, uh, confidences, you might say—uh—not about our very personal life but, you know, things like, like the—handling of the children—things like that—so—uh, now I feel calmed down to the extent that, us, I feel like I could go back to work—

(X. is again protecting his wife, by taking the blame instead of accusing her of making him late. However, this also enables him to interpret her silence as sympathy; if he doesn't take the blame, he fears losing this "sympathy." This is made clearer when he tentatively accuses her to his mother, and mother totally takes his side, denying anything positive with his wife—"everything is B.'s fault." At this, X. seems fearful that things have gone too far the other way, that his tie with B. is being destroyed, perhaps because of the intensity of his own unresolved feelings that this arouses.)

T.: You seem to have there some sort of a special feeling there about, uh, mentioning that your mother knows a lot about things—about your life with B.

X.: Well, my feeling is this—see, B.'s—B. was accusing me of being a mother's boy; that's one of her—things that she will not stand for, one of the reasons she didn't marry another person she met before she met me—how—to her it's despicable, and she got me to the extent where I admitted that I was a mother's boy; I mean she'd just badgered me—

T.: Made you—

X.: "The hell with you—I am a mother's boy, then, if you—"

T.: You just said this to get some peace, really?

X.: Yeah, in a way, that's right—and, uh, finally, when she did grab that and then really started, I said: "Well, damn you;

I am no mother's boy; if you think that—that I am," I said, "I am a human being, and I have my own opinions. I know I was raised by my mother, but what the hell am I supposed to be? Killed for that? Or what?" You know, "What can you hold against me for being raised by my mother? I didn't have a father"; so, uh, so I knew that—I had, uh—that was when she was talking about getting a trustee for the children—which I don't know anything about—I mean, I don't know how that could be arranged—

T.: It seems like you had a special—

X.: Yeah—

T.: Kind of a—you had a feeling—I got an idea from the way you looked when you were telling me about—how your mother knew a good bit about . . . the family, and I was just wondering what that feeling was—it seemed to mean something then.

X.: Well, I don't know, uh—well, I don't know what that would be except I thought if Mother didn't know too much, she wouldn't have stuck her nose in so much that—she—to get it burned, so to speak, by B.—

T.: Uh huh.

X.: And her father

T.: Maybe some sort of—

X.: She stuck her nose into (too?) personal affairs, such as—uh, oh, the way I do this and that—and, uh, and, uh, you see B. knew it and, uh, and, that's part of the reason why she—she's against her, because, uh—

T.: I was wondering if there was some feeling there that when you did bring up the matter of—it wasn't all your fault that you were late, that it had something to do with what B. wanted, that, in a way, this made trouble, too. Like there, again, there wasn't any way out for you—

X.: Well—uh—

T.: Like your mother seized on this not really to understand you or your situation, but—to stir things up between you and B. again.

X. (pause): That's right; that's it; maybe I didn't realize it, but I know that; I knew

she has been stirring things up between me and B. for a long time, if you put it that way—you know—she'd, uh, pass these comments about how incapable she was, and—and this and that—so—

(If X. turns to his mother, she uses *what* he says to attack his relationship with his wife. This increase of the conflict there obviously weakens him and makes him feel more dependent on mother. At the same time, his wife uses the *fact* that he goes to his mother, regardless of why or about what, to characterize him as a "mother's boy," although she is pushing him that way by putting so much off on him herself. It is a sort of double bind involving his relationship with two people, each focusing on only one level of his behavior, in the way least favorable to him, and rejecting his efforts to say there is something more to the situation, which they ignore.)

T.: Well, it sure seems like (here X. interrupts)—

X.: With B., on the other hand, always saying: "We have to get closer together closer, and our love has to grow," and this and that—well, I start getting confused; I don't see how I can meet those conditions unless—I couldn't see—in other words, she—lately she's been saying, that, that, that, uh, it depends on our love; it depends on—I don't mean intercourse; on other words, love, whatever it might, I can't even define the kind of love she means—

T.: It's not really clear what she is really talking about.

X.: Well—

T.: When she says this—

X.: That we have to understand each other, and love one another, and, uh, become two bodies in one soul; and, uh, well, you see that's kind of hard—uh—that, that's setting up a pretty rigid—uh—qualification.

T.: (pause): Maybe you feel that has a little bit of flavor, that she wants you just to go along with her in everything—

X.: Yes, and I imagine that's what I finally, finally concluded; I've been fighting it for years—I always wanted to have my own way—and that's why I always told her that if I decided to go to church, I might go to a Methodist church; I always wanted that out for myself, because I never, never would agree—completely; I said: "I might become

a Catholic, but don't count on it—when mother dies"; y' know, they knew mother was against it. And so all—all that she's gotten, she's got from this, hate from my mother—I imagine I—without meaning to, I'd—nurtured it, I'd given reason for that hate; in other words she thought if she could get mother out of the way—who knows, then—then I'd swing to her, actually I—I didn't think so; I felt the most important thing was to keep a job, make sure the children had enough to be brought up on, and, uh—ourselves, com—comfortable—you know—

(The wife emphasizes more and more that he must not be a "mother's boy"—she quit going with one before; so the threat of abandonment is there—while making it almost impossible to be otherwise: If he turns directly to mother, he is one, according to her, regardless of conditions. If he turns to *her*, since she says they should get closer, she has laid out all the specifications; she would be dominant, making him a mother's boy. He tries to be a man by working, but she keeps him away from the job; so everyone thinks him inadequate as a man there, too.)

All this time, she, as mentioned earlier, has various sources of support in religion—father, fine phrases, like "closeness," and so on, that are culturally acceptable, or that she can put over by skillful definition as "good," while all his needs are defined as "weakness"—so successfully that *he* increasingly accepts this; perhaps his illness may itself be seen as a resolution by accepting such accusations even more.)

T.: Uh, well, as I—I think over what you tell me about—that night, it sure sounds like although you may have been involved in it to the extent of saying, "O. K., we'll stop at the convent, and you can talk to the nun," it sure does seem that once that was done, when you got home, everybody was—was giving you the devil and leaving you standing all alone, and the thing that you couldn't see any way out of at all—

X.: Yes, but that really shouldn't have disturbed me; I mean—that's one thing I can't understand, because—

T.: Why shouldn't it?

X.: Why should it? It's such a small item—

T.: Your father-in-law gives you hell and walks off; your mother gives you hell and won't listen; your wife stands there and

lets them give you hell and doesn't say: "I wanted to go to the convent, and that's why we're so late," and she walks off then—

X.: Well, possibly—

T.: I mean, you're getting hell from all sides and being left alone, to boot; it's a pretty rough situation.

X.: Well, I didn't look at it; I mean I know I'd—I felt it strongly, I know that; in other words, you know, sort of, sort of a surprise, it happened so quickly; well, what the hell is going on, you know—and then—(overlapping and indistinct here)

T.: Yeah, must have been pretty confusing, to—having all this just sort of fall down on me.

X.: It was a little confusing, but then I just thought: "Well, the hell with them!" That's what I thought; I just said: "Well, the hell with"—that's the way they feel—it shouldn't; I didn't think it'd bother me, but there is something deeper than that—uh, it's it seemed to—been a delayed reaction—in other words, I wasn't feeling good, even on that trip—

T.: Uh huh.

X.: In other words, I—I know I—I was having this feeling of confusion—so that was even before that argument—

T.: Just this may have been added on to—

X.: That's right—

T.: Something else, but at least it gives us a—a picture of how you were in a difficulty with that, and we can talk some more then on what may have preceded it—

X.: Yeah—

T.: Well, I'm glad you were able to tell me about that today—

X.: Well, I thought I told you this once before—

T.: No, I never had anything like this clear a picture of it—

X.: Well, I don't think it was—the—I—mean I wasn't sure—like I say, I didn't feel well before that even—

T.: Well, we don't have to say this situation is the cause of anything, if this gives a picture of a difficulty you were in—

O. K., X., I'll see you Monday. Hope you have a nice weekend.

X.: Thank you.

Comment

We would like to review and emphasize several aspects of the material that seem to us to have particular relevance to the life situation in which X. developed a psychosis, and to the therapeutic situation in which he reviews these matters.

Pattern of X.'s Life Situation.—We have mentioned above our concept of the double bind as a situation (1) in which a person is faced with contradictory messages, (2) which are not readily visible as such because of concealment or denial or because the messages are on different levels, and (3) in which he can neither escape nor notice and effectively comment on the contradictions. We have tried to point out in our comments that X. is repeatedly involved in such situations with the people most important to him. His father-in-law sends him out on errands and his wife delays him further, but when he is attacked by the old man for not behaving like a responsible person, X. can only see the criticism as a "paternal" interest in his welfare. X.'s mother in this same context, and though she does not get along well with the father-in-law, berates X. for upsetting his father-in-law; X. attempts to handle the situation by saying it is unimportant. X.'s wife, after making him late, retires from the scene, leaving him to face the blame; he *imagines* she is "sympathetic" and had to leave in order to care for their children. In other examples, he appears caught in similar binds by the joint behavior of two persons—as between wife and mother on the "mother's boy" issue, or even by one person's blatant contradictions, as when his wife successfully insists that deception was not deception because it involved the church.

It is evident in the interview what strain and difficulty situations of this sort recurrently produced for X., even though he is still trying hard to minimize or deny this.

Denial is his usual, though ineffective, technique for handling them.

However, as mentioned earlier, the double bind is not a simple one-way relationship but is an interaction in which both (or all) parties tend to be sharing important similarities of behavior, at least for relationships that persist over some time. This is rather clearly illustrated by the instance—not a unique example—in which X., when just succeeding in refusing his wife's unreasonable request to visit the nun, suddenly reverses and gives in, pseudobenevolently, if she "would like to." Clearly, X. does not fully want to get free.

This poses rather sharply the problem, "Why did X. and not his wife break down?" Since they were both caught up in a similar family situation, what visible difference in their handling of affairs might account for her continued social functioning and his failure and eventual psychotic break?

Who the Kept and Who the Keeper?
Mrs. X.'s Transactions.—It would be a simple matter to postulate that X. is genetically more disposed to schizophrenia than his wife, and hence was the logical one to break down under the stress of an unhappy marriage. However, there are other considerations which might be offered as data relevant to Mrs. X.'s being in the more emotionally fortunate position.

1. She has fairly severe epilepsy and is "entitled" to the kind of consideration that the husband longs for. It is possible, additionally, that her disorder offers other psychological gains; e. g., it will be recalled that shock therapy for schizophrenia arose out of the observation that schizophrenia and epilepsy were relatively incompatible.

2. She was actively religious and able to use her religion as a strong lever to get "one-up" on her husband, who appeared to be a religious renegade but was not completely free. Her religious activities additionally provided certain positive figures both in reality and in fantasy for her emotional support.

3. Her inadequacies as a wife and mother could be justified from the standpoint of her illness and from the fact that her own mother was dead. That she exploited the latter fact is revealed in her attitude toward the patient's relations with his mother. He was criticized for being a "mother's boy"; yet her dependent relationship to her aunt and to the nuns was accepted, and indeed sanctioned, by the patient.

4. The cultural concept of "a mother" carried a good deal of weight for the patient and caused him, his wife, and his father-in-law to be acutely aware of his responsibilities toward her.† The "mother" concept further provided a dilemma for the patient in that he was torn between his duty to his own mother and to the mother of his children.

Because of the conventional validity and unimpeachability of her rationalizations, and the similarity of her maneuvers to those of his own mother, the patient was almost totally unable to spot the contradictions in the wife's communications. Yet, of course, she was equally helpless to get much satisfaction from her relationship either with her husband or with her children; she was "successful" negatively rather than positively.

The concepts mentioned above are only a few related to observable features of the actual relationship that might be reviewed in reconsidering the problem of relative "ego strength" of the patient and of his wife. They suffer additionally from the fact that they are presented alone rather than in some stratified fashion, layered with the

† Perhaps it is relevant to note that statistics of hospital admissions for schizophrenia reveal that it is not until 40 years of age that the admission rate for women exceeds that of men. Additionally, prior to age 40 a sizable percentage of female admissions are unmarried or childless women. It is possible that more is involved in these statistics than the simple fact that the female schizophrenic-to-be does not marry or, if she does, does not tend to bear children. Some such women may find a protective component, mental-health-wise, in being a mother of young children, either in the positive cultural sanctions and values accorded motherhood as such, or in the children's absorbing the most malignant aspects of the interpersonal difficulties.

husband's and other relatives' own personality problems and interpersonal behavior. That is, in considering the nature of psychogenic stress and its relevance to the onset of a schizophrenic psychosis, it is necessary to review the type of perduring or predominant transactions that are occurring between the patient and the significant others in his immediate environment and their relation to the culture and to the patient's early past. Domination by weakness can be especially effective as a means of controlling the definition of the relationship if the person doing the defining is ill, female, or operates in a matriarchal environment. Thus, the patient's wife related to her father in such a manner as to appear submissive, like a good daughter; at the same time she was actively controlling him. § It is important also to note that the concept of a "good daughter" has a positive cultural evaluation, while the patient's being a "good boy" vis-à-vis his mother has a negative connotation. Although the wife's father made difficulties for her by his seclusiveness, irritability, and weak health, he was also busy catering to her needs and asked no more from her than the husband did. Who can say what might have eventuated if her father had died just prior to her marriage to the patient, and she had been robbed of the prototype for her dealings with her husband, as well as losing an ally in her marital struggles?

The Illusion of Alternatives: X's Transactions.—One aspect of being an American that receives attention from the public press is the freedom to do what one wants and to tell the other fellow to "go to hell." Americans, by reputation, are their own bosses and resent being told what to do. The stereotype is familiar, and in some ways resembles an attitude manifested by Patient X. and by

§ A dramatic picture of the apparently submissive daughter who gets her own way, while placing responsibility for her behavior on the parental figures to whom she is "obedient," appears in Ann Whitefield, Shaw's heroine in "Man and Superman." It should be noted, though, that Ann is perhaps aware of her manipulations, and to that extent responsible, in contrast to Mrs. X's irresponsible unawareness and denial of control.

a number of schizophrenics we have studied. Overlooking the actual circumstances of concealed contradictory influences, the patient particularly feels as if he is the master of his fate, and hence holds himself responsible for making wrong specific choices or decisions and is haunted by obsessive doubts as to what choice to make. Actually, there is only an illusion of alternatives, since by the very nature of the double-bind situation, the patient will be "damned if he does and damned if he doesn't."

For example, one of the major points in the interaction described by X. is his feeling that he must take the blame for his wife's making them late and that by doing so he minimizes the possibility of a fight between B. and his mother. He states that B. can't stand a mother's boy; yet by covering up for her, he becomes a "mother's boy." Additionally, she had told him that she had stopped going with a former suitor because she discovered he was a "mother's boy." She wants to get closer to X.—in her words, "to become two bodies in one soul"—but this means to X. a suffocating closeness in which she is the "one soul" and he is the "lost soul." He turns to his mother when he feels B. is suffocating him, but this only reawakens the same problem with his mother and allows B. to taunt him. That he feels between B. and his mother is exemplified in the statement: "I might become a Catholic when mother dies." His work makes him feel more like a man, but he accepts a situation that B. sets up, in which he is forced to choose between her and his work. His defaulting in her favor increases his father-in-law's contempt for him, and so the possibility of the two men sticking together fades. It is not adequate to see that X. has no satisfactory relationship within the family. Rather it is noteworthy how, for him, a troubled relationship begets further troubled relationships.

There is ample evidence that X. sees himself as weak and helpless, and, on the other hand, as a good guy, who tries hard and who suffers from being "too nice." He would

like some babying, but he marries a woman who despises weakness and utilizes helplessness to gain interpersonal power. He notes neither this contradiction in her nor its reciprocal in himself. Indeed, so long as X. accepts denials and concealments he is offered and acts according to the illusion of alternatives—as, of course, he is encouraged to do—the more the situation will tend to deteriorate. He tries to adapt to opposing manifest demands at different moments, instead of dealing with the over-all contradictions embodied. But as these varying apparent problems are at best merely tangential aspects of the real ones, X. does not succeed in satisfying the others who make the demands, does not achieve acceptance and satisfaction, and is progressively more involved in fluctuating and contradictory behavior himself. This only reinforces the reciprocal double-bind involvements between them all.

We are primarily concerned here not with why X. follows this unsatisfactory course and is unable to break out of it but, rather, with its nature and outcome. However, we may say, on the basis of additional interview material with X. and with other patients, that we assume that X. had countless experiences in his childhood, when his real dependency needs were great, that were prototypically related to the pattern described in this interview.¶ One such sequence from a nonpsychotic patient is described below because it was studied shortly after its inception and is probably more reliable than an adult patient's report of events in his childhood. The example appears as different only in degree from Patient X.'s experience.

A young adolescent who had a problem in not feeling like one of the boys, and who wanted to please his ineffectual father by becoming popular, returned home later than usual one day because he had been out with the gang. His enthusiasm for his new-found manliness was somewhat dampened when his mother greeted him with an underplayed "I

was worried to death about you" approach. There was an unpleasant feeling in his stomach, and an old ghost reminded him that he was capable of worrying mother and that she would be free from worry if it were not for him. This feeling was a kind of unconscious heroin for him because, though sickening, it produced grandiosity and a special sense of preciousness. As a consequence of the incident with mother, he renounced the pleasure of roaming the streets with the fellows and came home promptly for the next few days; but then one night mother announced at the dinner table that there hadn't been as many phone calls for him lately. He resented her doing this in front of father, but the signal from his stomach announced: "I am worrying her again." At this point he still attempted to solve the dilemma in terms of alternatives. These alternatives, stated roughly, were: "Should I spend more time at home or more time with the boys?"

Being still unsure, he returned home promptly the next day, only to find that mother had gone uptown and had left a note telling him so. Here was an opportunity to break the bind they were in, but it is in the nature of these reverberating cyclic sequences that he could not pull out. Instead, he stayed around the house and surprised mother when she returned by having started dinner. There was some mutual uneasiness about the "pansy" implications of his cooking dinner, but this was handled (as so many things had been in the past) by a covert agreement not to mention it to dad. And so the cycle was perpetuated.

The Psychotic Break.—While we are unable to state at what precise point a psychosis eventuates in X. or any other patient, it does seem to relate to the frequency, intensity, and timing of double-bind sequences. Constitutional factors, external stresses, and the experience of a previous psychosis are also possible contributory factors. We shall consider here the question of what sort of change in response pattern is X.'s development of psychosis,

¶ Some consideration of the general etiology of such double-bind involvement is given by Bateson, Jackson, Haley, and Weakland.¹

and what factors one can see that appear to have been temporarily related to it.

X.'s way of alternating conciliatory "good behavior" with occasional and abortive rebellious assertion does not gain him any control in his relationships, and indeed produces the opposite result. We can assume that his inability to deal with his wife's control through helplessness may have produced a covert competition with her that becomes manifest and explicit when he becomes psychotic. This is not to say that X. deliberately becomes psychotic to get attention. Rather, viewing the matter in terms of communication, as X. more desperately and unsuccessfully attempts to gain some control and satisfaction in his relationships, but fails with ordinary verbal means, his level of communication shifts. Thus, when he cannot separate the letters, he does not feel talking will help any, but he pales and a fellow worker notices he *looks* sick.¶ Yet X. goes even further, into psychosis. Several factors may be significant for this ultimate development.

1. X. escaped his job problem by illness but felt his family problems remained, just as they did after feigned illness the day before.

2. It seemed, though, that some fortuitous, unplanned change at the level of physical objects, e. g., an auto breakdown, might alleviate the family struggle. Hallucination at least subjectively fits this specification.

3. He had already had an experience of a psychotic break; so this path was to some extent marked out for him. #

¶ This shift may be compared with an example of culturally different levels of communication in social excuses pointed out by Margaret Mead: A Russian would not excuse himself from a party he did not wish to attend by reporting a non-existent headache, about which he might then feel guilty. This is more characteristic of an American; a Russian would just have the headache!"

It is striking to notice that if X.'s retrospective account is accurate, his psychotic break involves at least three specific instances of idea and realization. He claims illness, then gets sick. He wishes for something wrong with the car, then sees the peculiar taximeter. He tells his wife "You're driving me crazy," then breaks.

Becoming psychotic does put X. at once in a position of maximum helplessness, because he is crazy and unable to do anything, while at another level it also gives him much more control. If he is more helpless than his wife and others, they *must* now take care of him. It is evident that as he becomes psychotic, the family members alter their behavior toward him, a change which he could not get them to make before.

Accompanying this alteration of relationships, and paralleling it in important respects, is a great alteration in X.'s perceptions and conceptions. This is the aspect of psychosis that has received the most attention from investigators. However, it is essential to see, as this interview illustrates, that X., in becoming psychotic, does not shift from perceiving correctly to "distorting reality." X.'s observations and communications are distorted before his break, and are differently distorted afterward.

Prior to his psychosis, X. is maintaining a very special view of the world in his illusion of alternatives, an "either-or" way of regarding relationships. Particularly, he is distorting perceptions of his social world, the most fundamental "reality" for human beings. He is oriented to the material world and to limited transactions, but not to contradiction between levels or modes of behavior. When he hopes for an accident to the car to provide him with an excuse for being late, he is on the slippery edge beyond which the material world gets distorted to provide hoped-for interpersonal gain.

When he becomes psychotic, he distorts material "reality," as with the taximeter, and more limited social situations, as in his feeling watched at work. These distortions are more easily recognizable by the rest of us. Yet at the same time he sees certain feelings and relationships more clearly than in his prepsychotic state. A patient who has felt guilty because he is not a good enough son and who, when he becomes psychotic, expresses concern over mother's suicide potential is not just expressing hostility but is

acknowledging mother's depressive tendency.

Such insights are a mixed blessing, however. The patient can see and speak important truths because he is "sick" and out of the situation. But these perceptions are difficult to integrate because, since he is crazy, they do not count and others do not respond to his communications as messages to them. The so-called "social recovery" is the prime example of a person who manages to disregard a whole class of percepts by labeling them as his previously crazy self.

As mentioned earlier, it is not possible to establish with certainty the specific nature and circumstances of X's psychotic break. However, the available evidence suggests that after a long build-up of stress there was a fairly sudden and sharp break into overt psychosis. This seems to have occurred at a time when X's existing practice of denial and distortion of interpersonal realities was becoming inadequate to avoid choice and action, or, put with a different emphasis, when he was closer to being able to see his true situation, but not able to face it. Thus, on the day before his break, all of those most significant to him were attacking him in ways which must have made their contradictions especially blatant and hard to overlook, while simultaneously making it impossible to turn from one of them to another, as before, for even temporary support. Other available data also suggest that, despite his difficulties, X. recently had been making some progress in his job. Just at this point his wife attacks this by making him late. Was it becoming so clear that she did not want him to succeed that he could not, short of psychosis, fail to see this?

Then came the last straw, the matter of sorting the letters. This situation is an incredible parallel to X's dealings with interpersonal problems by the illusion of alternatives, as the problem with the letters is to make a correct choice between two polar alternatives. X. does not see that his personal alternatives are not real ones, or that there are not really two distinct kinds

of letters but only arbitrary definitions. With the letters he must make a choice and cannot use the denial-and-avoidance techniques he employs with people. This appears to be that point at which he shifts from attempting to "solve his problems" to becoming "sick," whereby he is admitting he cannot solve them. He describes the sequence beautifully.

1. He felt they were watching him, as if waiting for him to make a mistake. (Later he produces something—paleness—and they do watch him.)

2. An apparently simple task separating the long letters from the short ones turned out to be impossible because of the in-betweens. In-betweens are not allowed.

3. He became increasingly critical of himself. This had worked to some extent in relating to people; it was ineffective with the letters.

4. The turning point was an involuntary behavior, which others noticed, and responded to. He became visibly ill and was told: "If you don't feel right, why don't you go home?"

5. Even the shift into the frame of illness was not enough, because all the way home he worried: "How can I explain this to them?"

6. Psychotic delusions allowed him to free himself of decision making. For example, the cab driver is a hospital attendant in disguise. There is no problem in "home" vs. "hospital"; it has been resolved.

The Interview Situation, and Psychotherapy.—It is perhaps unexpectedly rewarding to raise the question: "Why did this interview centering on X's break take place just when it did?"—what were its circumstances? In no previous interview had he discussed this matter in any such detail, and in this one it was not brought up deliberately as a topic. Rather, the therapist merely followed up with some persistence the patient's early remark that his current difficulties about leaving the hospital are "just about the same question" as "why did I have the nervous breakdown in the first place?" The parallel situation in the present is his attempting to

make a sharp choice between staying in the hospital or going home, while feeling helpless to do so. He fears that his fate really may be controlled by conflicts between others—the therapist and the ward doctor, and, beyond them, his wife and his mother again. He feels like a pawn in their games, but he now trusts the therapist enough to bring up his concern. Talking about his psychotic episode, although promoted by emotional and relational similarities, seems also to depend on at least three current differences from the old situation. 1. There is some real difference in the persons immediately involved and their behavior. The therapist and ward doctor at least present him with less concealed contradictions than his family members did. 2. Beyond this, also, the situation is less crucial for him; it is more limited and the persons involved less important. 3. He believes in doctors and accepts to a large extent that they are trying to help him. By talking about his hospital situation, he is working through an “artificial” psychosis, similar to the real one but more manageable. A parallelism with the Freudian idea of “transference neurosis” is evident here; however, analytic thinking usually plays down the role of the actual therapeutic situation.

We feel that the similarity of circumstances between original significant events and their re-creation, review, and reworking in therapy is crucial, and is not confined to the session presented here. Especially, although detailed exposition and evidence must await later publications, we believe that something resembling the “double bind” must often be instituted on the patient by the therapist to obtain therapeutic change. This “therapeutic bind,” however, must also differ in such a way as to require not the distortion, denial, or unawareness of the nature of vital interpersonal relationships of the patients but, rather, increased awareness of their true nature. Such awareness stands in contrast to both X.’s private distortions and Mrs. X.’s special manipulation of public stereotypes. It may not always be

necessary. For example, in stable social contexts habitual patterns of behavior may serve to establish and regulate relationships in a reasonably satisfactory way. Thus, ordinary everyday relationships among “normal” people often do not involve much conscious awareness of their nature as such. But unsatisfactory relationships, with no mutually fitting behavior and views in important situations, may arise from social changes, cultural contacts, and individual idiosyncrasies. Then increased awareness may be an important means of locating interpersonal dissatisfaction and making adaptive changes in relationships.

Conclusion

We present a transcribed interview in which Patient X., recovering from a schizophrenic episode, is describing the circumstances surrounding his psychotic break. We attempted to demonstrate that, despite the absence of any horrendous or earth-shaking occurrences, X., because of the circumstances of his rearing and current living, was under a very great stress. He was caught up in a series of self-perpetuating transactions, which we label “binds” because they inflexibly involve two people in a dissatisfying amalgam. X. attempted to solve his interpersonal difficulties as though they were solvable if he could but make the right choice. This method, the illusion of alternatives, developed out of his inability to comment upon (notice) mutually contradictory multilevel communication sequences. His subsequent psychosis we see as restitutive, since his being “sick” encloses his attempts to form relationships within a new frame and allows him to view what he has been avoiding.

It is important to restate that we do not see X. as having gotten “sick” (psychotic) in order to break the bind. The change is not voluntary, and the psychotic state and the being “sick” create a new set of problems as formidable in some ways as the previous ones. X. starts the interview by indicating that all is not well with his hospitalized self.

He fears the re-creation of the problems that drove him to the hospital in the first place. Fortunately, because of the therapeutic relationship, he can voice his doubts and fears and make some sense of them. The old ties are still operating, and X. must also face another failure (his job and having to be hospitalized), so that he pays dearly for his new insights. He tells the therapist in effect: "What is a man profited, if he shall gain the whole world, and lose his own soul?"

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Ascorbic Acid Level and Lag Time in Oxidation of N,N-Dimethyl-*p*-Phenylenediamine

Correlation in Sera of Normal Controls, Psychotic Patients, and Animals

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Introduction

Recently Akerfeldt reported that the sera of patients with certain mental disturbances (schizophrenic, manic-depressive, and senile psychotic reactions) had the capacity to oxidize N,N-dimethyl-*p*-phenylenediamine dihydrochloride (DPP) more rapidly than fresh sera obtained from healthy normal subjects.^{1,2} He suggested that the lag period in the oxidation of DPP by normal sera was probably due to a reducing substance, most likely ascorbic acid.

This relationship has been examined in the present report. Data will be presented to show that there is a correlation between serum ascorbic acid and the lag period in the oxidation of DPP by sera from the normal as well as the schizophrenic human subjects used in our study. It will be demonstrated that this relationship also exists in the case of dogs and rabbits.

The validity of Akerfeldt's formula for determining the ascorbic acid content of serum from the measurements of the lag period in the oxidation of DPP and the slope of the curve describing the rate of oxidation of the compound by serum was also investigated.

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A preliminary report of a portion of these data was read to the 124th Meeting of the American Association for the Advancement of Science, Indianapolis, Dec. 28, 1957.

Experimental Study

The N,N-dimethyl-*p*-phenylenediamine dihydrochloride was prepared from the monohydrochloride.* The procedure suggested by Akerfeldt¹ for following the oxidation of DPP was used except for one modification. In order to maintain the final pH of the reaction-mixture in the range of 7.00 to 7.15 at all times, it was necessary to use 1.4 ml. of serum with 1.6 ml. of a 0.1% DPP solution. The blank was prepared by using an identical amount of serum with 1.6 ml. of phosphate buffer in order to produce the same pH range in the final mixture. All optical density measurements were made at 552 m μ . It should be noted that the slight variation in the original Akerfeldt method resulted in shorter lag periods.

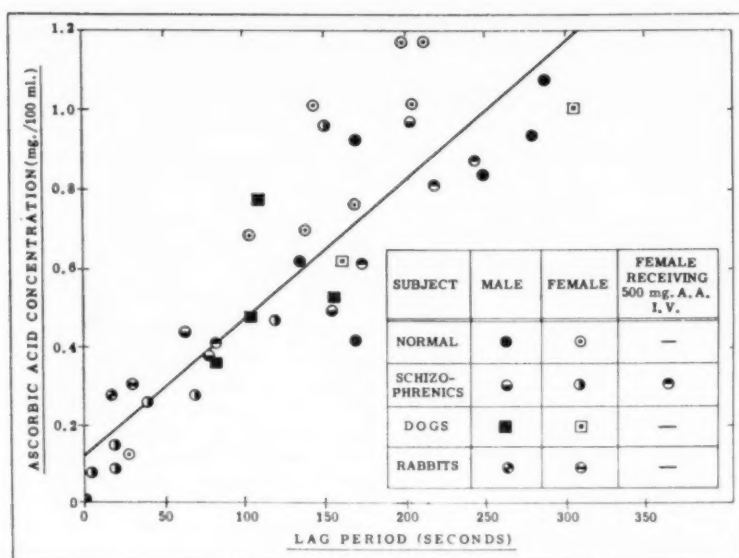
The ascorbic acid was determined by the method of Mindlin and Butler,³ modified to the extent that the procedure was adapted to the Beckman spectrophotometer when 1.0 ml. of serum was used. The optical density for this determination was measured at a wavelength of 514 m μ .

At least 12 ml. of blood was withdrawn from fasted patients, fasted control subjects, and the animals. Dogs were chosen for convenience, although other animals probably present similar findings, as was found to be true in the case of two rabbits studied to date. The serum was separated from clotted blood by standard procedure, extreme care being taken to prevent hemolysis. Proper aliquots from the same serum sample were then used to determine the ascorbic acid level, as well as the rate of oxidation of DPP.

Results

When Akerfeldt's formula for determining the ascorbic acid content of serum was applied to the data on normal and schizophrenic patients, it was found that in only about 30% of the instances were the calculated results within 10% agreement of the experimentally determined values. In

* Eastman Kodak Company.



Relationship of the ascorbic acid level and the lag period in the oxidation of N,N-dimethyl-*p*-phenylenediamine dihydrochloride (DPP) by sera from 14 normal controls, 16 patients suffering from schizophrenic reactions, 6 dogs, and 2 rabbits. (The black dot at the intersection of the axes [o point] represents a schizophrenic female.)

some cases the deviations were as great as 60%.

In the Figure the serum ascorbic acid concentration, expressed as milligrams per 100 ml. of serum (ordinate), is plotted against the lag period, in seconds (abscissa), observed during the oxidation of DPP by an aliquot of the same serum sample as that used in the ascorbic acid assay. The data were obtained using the sera of the following four groups: (a) 14 controls, consisting of 8 women and 6 men, all young, healthy normal adults; (b) 16 young, physically healthy patients who were admitted to an acute psychiatric treatment center (Larue D. Carter Memorial Hospital, Indianapolis) with illnesses diagnosed by their physicians as schizophrenic reactions; (c) 6 dogs (4 male and 2 female), and (d) 2 rabbits (1 female and 1 male). The patients consisted of 12 women and 4 men; 4 of the women were given 500 mg. of ascorbic acid intravenously approximately 16 hours prior to biochemical analysis.

The curve drawn through the data was determined by the method of least squares.

It demonstrates a positive relationship between serum ascorbic acid levels and the lag period in the oxidation of DPP in our groups of normal controls, psychiatric patients, and animals. The coefficient of correlation was found to be 0.87.

Of the 12 patients who had not received ascorbic acid prior to the biochemical analysis of the sera, 8 showed both low serum ascorbic acid levels (between 0 and 0.44 mg/100 ml.) and short lag periods (less than 80 seconds). Data from the other four patients—one of these (a woman) being markedly improved and receiving weekend home-leave privileges and two (men) on electroshock treatment—are also included.

The data on 14 normals revealed that 12 had ascorbic acid levels in the 0.62 to 1.18 mg/100 ml. range, 1 at the 0.42 mg/100 ml. level, and 1 at the 0.13 mg/100 ml. level. The lag periods varied from 110 to 300 seconds, with one exception. This was in the case of a woman with the lowest "control" ascorbic acid level and with an unusually short lag period, of 30 seconds.

ASCORBIC ACID LEVEL AND LAG TIME IN OXIDATION OF DPP

Summary of Effect of Ascorbic Acid Administration on Blood Serum Levels and Lag Period in Oxidation of DPP

EXP.** IDENTI- FICATION	ASCORBIC ACID ADMINISTERED	SERUM ASCORBIC ACID LEVEL FOUND (mg./100 ml.)		Δ AA*	LAG PERIOD (SECONDS)		Δ LP*	$\frac{\Delta \text{AA}}{\Delta \text{LP}} \times 100$
		BEFORE	AFTER		BEFORE	AFTER		
PATIENT 1 (S)	500 mg. I. V.	0.09	0.24	0.13	21	78	57	0.23
PATIENT 2 (S)	500 mg. I. V. 500 mg. Oral	0.08	0.38	0.30	0	42	42	0.75
PATIENT 3 (S)	500 mg. I. V. 500 mg. Oral	0.61	1.72	1.11	141	252	111	1.00
PATIENT 4 (S)	500 mg. I. V. 500 mg. Oral	0.23	0.78	0.55	52	99	47	1.17
NORMAL (N)	500 mg. I. V. 500 mg. Oral	0.54	1.50	0.96	176	279	103	0.93
NORMAL (N)	500 mg. I. V. 500 mg. Oral	---	---	---	160	270	110	---

* Δ AA = CHANGE IN THE SERUM ASCORBIC ACID LEVEL

Δ LP = CHANGE IN THE LAG PERIOD

** S = SCHIZOPHRENIC

N = NORMAL

In the data on the animals, it was found that the two rabbits had low ascorbic acid levels (as compared with the data on the normal human controls), as well as short lag periods. In the dogs ascorbic acid levels and lag periods fell in approximately the same ranges as the data from the normal male controls.

In the Table several experiments are summarized in which the effect of ascorbic acid administration 16 hours prior to testing on blood serum ascorbic acid levels and corresponding lag periods in the oxidation of DPP was explored. In every instance, as the ascorbic acid level rose, the lag period increased.

Comment

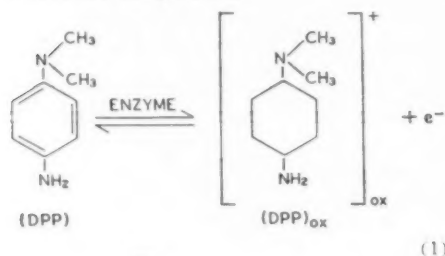
Akerfeldt's work has suggested that there is a difference in the way N,N-dimethyl-*p*-phenylenediamine dihydrochloride is oxidized by serum from normals and by that from patients with mental and emotional disturbances, especially the acute schizophrenic patient. This work was confirmed by Abood.⁴ However, these workers found

no clear-cut demarcation when comparing their data, since overlapping occurred among the groups. Heath and Leach⁵ also found this to be true in their test (oxidation of epinephrine).

Recently, Horwitt et al.⁶ concluded, after applying the Ravin,⁷ Abood,⁸ and Akerfeldt¹ tests to normal and schizophrenic adult patients, that tests involving the oxidation of phenylenediamine or its derivatives in their present form are not good enough to distinguish between such groups. Aprison and Drew⁹ came to the same conclusion after studying children who had been diagnosed as being schizophrenic and confined to a mental hospital. Nevertheless, there was a marked difference in the way some samples of serum were able to oxidize DPP.

In the case of the normal, nonpregnant human, a lag period occurs prior to the oxidation of DPP by the serum. The lag period was thought to be due to a reducing substance.¹ It was suggested that when this substrate (DPP) was oxidized (probably by ceruloplasmin), the DPP_{ox} reacted with ascorbic acid to yield the original DPP and

dehydroascorbic acid. Equations 1, 2, and 3 describe the process.



Ascorbic acid $\xrightleftharpoons[-2\text{H}]{+2\text{H}}$ dehydroascorbic acid \rightarrow diketogulonic acid (2)

2 [DPP]_{ox} + ascorbic acid \rightarrow 2 [DPP] + dehydroascorbic acid (3)

Consequently, as long as there is any ascorbic acid available to participate in Reaction 3, DPP_{ox} is reduced back to the non-colored form, DPP. This suggests that the ascorbic acid content of the serum should be related to the lag period in the oxidation of DPP. Furthermore, if this hypothesis is true, then the higher the ascorbic acid content the longer the lag period. The data in this paper are consistent with this point of view.

It was also noted that the relationship existed when the experiments were done with dog and rabbit sera. In fact, it is interesting to note the impressive interspecies similarities.

As has been pointed out above, the formula suggested by Akerfeldt for determining serum ascorbic acid levels from the measurements of the lag period and the slope could not be substantiated in the majority of our determinations. Therefore it would appear that in vivo the correlation between the observed ascorbic acid level and the product of slope and lag period is of a lower order than that between the observed ascorbic acid level and the lag period. Here it is pertinent to stress, however, that under certain conditions factors other than ascorbic acid levels influence the reaction. These are currently under investigation in this laboratory.

Since the majority of patients in our experiments whose illnesses were diagnosed

as schizophrenic reactions did exhibit short or no lag periods in the oxidation of DPP, it may be that the ascorbic acid metabolism in these patients was impaired at some point. Since it was possible to alter both the lag period and the serum ascorbic acid level by exogenous ascorbic acid, it appears that the schizophrenic patient is capable of oxidizing DPP after the usual "normal" delay, provided the serum ascorbic acid level is adjusted to normal values. This may suggest the obvious mental-hospital-diet hypothesis, but perhaps this explanation may be too simple. On the other hand, Horwitt¹⁹ has reported that blood ascorbic acid levels in hospital patients are low and recently found⁶ that of 34 schizophrenic patients, 16 had levels of less than 0.5 mg/100 ml. In the present study the ascorbic acid levels in 9 out of 12 patients fell below this level.

The answer to the question why the ascorbic acid level tends to be so low in certain schizophrenics is challenging, but beyond the limits of the present report.

Summary

A positive correlation is shown to exist between the lag periods in the oxidation of N,N-dimethyl-*p*-phenylenediamine dihydrochloride and the serum ascorbic acid concentrations in 14 normal controls, 16 patients with diagnoses of schizophrenic reactions, 6 dogs, and 2 rabbits. Compared with normal controls, the lag periods and the serum ascorbic acid levels were on the whole lower in hospitalized patients. Administration of ascorbic acid to a number of normal controls and schizophrenic patients produced, in all instances, a prolongation of the lag period. Akerfeldt's formula for determining serum ascorbic acid levels could not be substantiated in the majority of the determinations.

D. B. Manhart and P. B. Kirk gave technical assistance.

Indiana University Medical Center, 1110 W. Michigan St. (7) (Dr. Aprison).

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Studies in the Effect of Lysergic Acid Diethylamide (LSD-25)

Self- and Object-Size Perception in Schizophrenics and Normal Adults

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This study is one of a series of experiments designed to inquire into some of the perceptual effects of administration of lysergic acid diethylamide (LSD-25)* to schizophrenics and normal adults. Specifically, the study deals with the effect of LSD on size perception of one's own body and objects in space. This problem is approached within the framework of organismic behavior theory, viz., the sensory-tonic field theory of perception and the developmental theory.

According to the sensory-tonic theory, perception is an experience that corresponds to a particular relation between the organismic state and the impinging stimulus. From this general formulation it follows that a change in either the external stimuli or the organismic state will produce a change in perception. That alterations in organismic state produced by LSD are reflected by changes in perception has been demonstrated by us in another experiment, concerned with perception of verticality (with the same groups of subjects), reported in this journal.¹ The observed

changes in perceptual organization within the normal group were found to be in the direction of greater primitivity; with the schizophrenic group the drug served to produce perceptual regression to an even greater degree than was already present.

The present study inquires whether these effects of LSD can be generalized with respect to other perceptual properties, viz., size. The study deals with the perception of size with respect to two referents, i. e., size perception of one's own body or body parts and size perception of external objects in space. In considering the primitivizing effect of LSD, the question may be raised whether or not this effect of primitivization differs for the two kinds of objects, viz., the self versus external objects. If we follow Schilder and other students of body image, we are led to the conclusion that the perception of one's own body in contrast to the perception of external objects is much more labile, more subjected to the flux of organismic happenings.²

It is therefore reasonable to assume that primitivization due to the drug will be manifested to a greater degree in the body perception, with its greater lability, than in the more stable perceptual external objects.

The specific hypothesis of the study is derived from some of the above considerations, as well as from some empirical results dealing with effect of contour on head size³ and from the assumption that LSD operates as a primitivizing agent. In an earlier study it was found that perception of head size decreased when a contour was introduced by lightly touching the subject's

From Clark University.

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Harry Freeman, M.D., Director of Research, Worcester State Hospital, cooperated in this study, and Herbert Cline, M.D., gave assistance.

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*Lysergic acid diethylamide (LSD-25) is an ergot derivative, belonging to the ergonovine group. It was first isolated in 1938 by Stoll and Hofmann.⁴

temples. Contrariwise, it may be assumed that with the lessening of the definiteness of the boundary of the body in relation to the surroundings, there is an increase in perceived size of the body. Given this assumption, as well as that concerning the primitivizing effect of LSD, it seems reasonable to make the following inferences: Should primitivization exert itself in terms of dedifferentiation of self and environment, we might expect that LSD would operate in terms of lessening the boundaries between the object (in this case the body) and the environment in which it is embedded, which, in turn, would make for an enlargement of perceived size of the body. Given the above considerations, it is expected that under the influence of LSD there will be an increase in the perceptual size of one's own body with little or no change in the perceived size of external objects.

Three experiments were carried out with schizophrenic and normal adults. Experiment I was concerned with the effect of LSD on head size and size of various external objects; Experiment II was concerned with the effect of LSD on estimates of arm length; Experiment III was concerned with the effect of LSD on size of drawings of the human figure.

In all three experiments two groups of subjects were used: Group I consisted of 18 hospitalized patients, 11 men and 7 women, with a diagnosis of schizophrenia. The distribution of subjects in terms of diagnostic classes was as follows: chronic undifferentiated, eight; paranoid, five; acute simple, four, and hebephrenic, one. All subjects were free of any visual defects or physical disabilities. Their mean age was 35, with a range of 23 to 47 years. The median length of time spent in the hospital was three years three months. The second group of subjects consisted of 18 normal adults, 11 men and 7 women, with ages ranging from 21 to 38.

Within each of the two groups one-half of the subjects were tested first under LSD

and then without LSD; the other half were tested in the reverse order; the two sets of conditions were carried out six to nine days apart. Normals and schizophrenics were treated in identical fashion except for the dosage levels of LSD. For normals the dosage was 40 μ g. (0.04 mg.), except for two subjects, who received 25 μ g. For schizophrenics, the dosage was greater; namely, 14 received 100 μ g., 1 received 150 μ g., and 3 received 200 μ g.

Experiment I: Effect of LSD on Head Size and Size of External Objects

Material and Method.—The task for S was to indicate the size of his head, as well as that of various external objects by the following device: The device consisted of an adjustable frame which could be made narrower or wider, or taller or shorter, thus exposing a greater or smaller area of a white background. The variation in the horizontal and vertical directions was accomplished independently by two sliding black panels. The device thus permitted variation of the rectangular white space in the horizontal and vertical directions. The task for S was to instruct E to open the two black panels so that a white space showed which appeared to him to be the equal in size of the object named. The horizontal panel was always moved first from a closed position so that the minimal white space was visible. The vertical panel was then raised until S instructed E to stop. After this, S was permitted to have the panel moved in one or the other direction until he was satisfied that the white space appeared equal in size to the object named. The objects which S was required to estimate were as follows: a dollar bill; a 10×10 in. square; a regular-sized pack of cigarettes; a \$20 bill; a frame for S's head. The instructions, as to the estimate of the subject's head size, were for S to make the opening just large enough for him to squeeze his head through, so that the black frame would just touch both of the temples, the base of the chin, and the top of the head.

Results.—Normals: The mean size estimates of the head and four external objects, with and without LSD, along with *P*-values of significance of difference between means are given for the normal group on the left side of Table 1. Examination of the Table shows that perceived head size, as measured by width and area, increases significantly under LSD, and height estimates increase,

TABLE 1.—Effect of Lysergic Acid Diethylamide on Size of Body and External Objects

Object	Normals Means, Cm.			Schizophrenics Means, Cm.		
	No LSD	With LSD	P	No LSD	With LSD	P
Head size						
Height	21.1	21.8	>0.05 *	20.3	21.8	<0.01
Width	18.0	18.9	<0.05	17.5	18.2	>0.05
Area	386.0	415.8	<0.05	361.5	410.2	<0.05
Dollar bill						
Height	5.2	5.3	>0.05	5.4	5.5	>0.05
Width	14.8	14.5	>0.05	14.7	14.7	>0.05
Area	76.9	77.7	>0.05	79.8	81.9	>0.05
\$20 bill						
Height	5.1	5.2	>0.05	5.3	5.4	>0.05
Width	14.8	14.5	>0.05	15.6	15.2	>0.05
Area	76.6	76.0	>0.05	88.0	83.8	>0.05
10"×10" square						
Height	20.1	20.5	>0.05	18.3	19.2	>0.05
Width	22.6	22.9	>0.05	22.2	21.1	>0.05
Area	459.0	481.6	>0.05	421.9	431.0	>0.05
Pack of cigarettes						
Height	6.2	6.4	>0.05	6.4	6.5	>0.05
Width	6.2	6.1	>0.05	6.3	6.4	>0.05
Area	38.8	39.4	>0.05	40.7	42.0	>0.05

* $F=4.13$; for significance at the 0.05 level F would have to be 4.45.

though not significantly; LSD has no significant effect on the size of the four external objects, though in general there is a slight increase in over-all size (area) for three of the objects.

Schizophrenics: Examination of the right side of Table 1 shows that under LSD perceived head size, as measured by height and area, increases significantly and that width increases, but not significantly. Similarly, as in the results for normals, under LSD there is no significant increase in perceived size of the four external objects, though in general there is a slight increase in over-all size (area) for three of the objects.

Experiment II. Effect of LSD on Perception of Arm's Length

Material and Method.—The task for S was, in a darkroom, to instruct E to place a luminescent marker at a distance from S's body which corresponded to where his finger tips would be if his arm were fully extended straight out in front of him. The apparatus essentially consisted of two parallel luminescent lines placed in a horizontal plane and extending from S's chest straightfor-

ward away from him. The strips were 200 cm. long and 2 cm. wide, and were separated by a distance of 7.5 cm. The marker consisted of a luminescent oblong, which could slide along the luminescent markers. The distance from S was measured by means of a ruler. Four trials were employed: In two of the trials the movable indicator was started at the body; in two the movable indicator was started 200 cm. away from the body. A fixed sequence of starting positions was employed, namely, starting at the body, starting away from the body.

Results.—Normals: The mean estimates of arm length with and without LSD are given for normals in the left side of Table 2. The mean arm length is significantly greater under LSD than without LSD.

Schizophrenics: The mean arm's-length estimates under LSD and without LSD for schizophrenics are shown on the right side of Table 2. The trend here is the same as that obtained with the normals; i. e., there is an increase in estimate of arm's length under LSD as compared with that without LSD. However, this difference is not significant. When the results are separated according to the two starting positions, an

TABLE 2.—Effect of Lysergic Acid Diethylamide on Perception of Arm's Length

		Normals Means, Cm.			Schizophrenics Means, Cm.		
		No LSD	With LSD	P	No LSD	With LSD	P
Starting position	Near	65.7	66.3	>0.05	65.1	64.3	>0.05
	Far	69.8	76.7	<0.01	58.0	80.6	<0.01
Over-all		67.8	71.5	<0.01	66.6	72.5	>0.05

EFFECT OF LYSERGIC ACID DIETHYLAMIDE

TABLE 3.—Effect of Lysergic Acid Diethylamide on Size of Human-Figure Drawing

"Draw-A-Person"	Normals Means, Cm.			Schizophrenics Means, Cm.		
	No LSD	With LSD	P	No LSD	With LSD	P
Length of figure						
Same sex	16.2	17.5	>0.05	18.7	22.0	<0.01
Opposite sex	16.2	17.3	>0.05	20.8	25.0	<0.01
Width of shoulders						
Same sex	3.8	4.2	>0.05	4.7	6.0	<0.01
Opposite sex	3.3	3.7	>0.05	5.4	6.7	<0.05
Length of head						
Same sex	3.2	3.4	>0.05	5.0	5.3	>0.05
Opposite sex	3.1	3.5	>0.05	4.9	5.5	>0.05
Width of head						
Same sex	2.7	3.2	>0.05	4.6	5.1	>0.05
Opposite sex	2.3	2.8	>0.05	4.6	5.3	<0.05

interesting difference is found. A significant trend is observed for the starting position away from the body; i. e., under LSD the arm's-length estimate is markedly greater than without LSD. However, when the starting position is close to the body, this trend is not maintained. This discrepancy is undoubtedly related to the interaction between increased starting-position effects under LSD and increased perception of arm's length under LSD.

Experiment III: Effect of LSD on Size of Drawing of the Human Figure

Materials and Method.—S was seated at a desk. In front of him was an 8½×11 in. sheet of white paper and a #2 lead pencil. He was asked to "draw a picture of a person." After he had completed the first picture, he was required to draw a person of the sex opposite that of the first drawing. Four measures were employed for each of the two drawings: total length of drawing; length of head; width at shoulders; width of head (ear to ear). In the two cases in which S drew profile pictures, under both the LSD and the no-LSD conditions, the width of the body at chest level and of the head at the nose level was substituted. In two instances S drew a profile under LSD and no profile without LSD. In this case, comparable measures could not be employed, and therefore the cases were dropped from the particular analysis.

Results.—Normals: The results are presented for normals with and without LSD on the left side of Table 3. For all eight comparisons (four measures on each of the two pictures) an increase in size of drawing was obtained under the condition of LSD. These increases varied from 6% to 22%, though they were not significant.

Schizophrenics: Examination of the right side of Table 3 shows that the schizophrenics increased the size of their drawings under conditions of LSD. An increase was obtained for each of the eight measures, and for five of these measures there was a significant increase.

Comment

The findings support the hypothesis that under the influence of LSD there is an increase in the perceptual size of one's own body, with little or no change in size of external objects. As will be recalled, this hypothesis is derived from the assumption that LSD serves as a primitivizing agent. The increase is restricted to the size of one's own body and its parts; no significant differences were found for changes in the size of external objects following administration of the drug. As stated previously, this finding is in keeping with the interpretation that the primitivizing effect of the drug operates optimally on objects such as the body, which by their nature are less differentiated from the surroundings and in that sense are less stabilized. This interpretation is in keeping with the findings of other studies. One such study is that of Rosenblatt, who worked with manic and depressed hospitalized patients and utilized drawings of the human figure, as well as various geometric forms.² Rosenblatt's findings are pertinent to the present study insofar as there were differences in size perception, depending upon organismic state (elated versus depressed), for representations of the human figure but no such dif-

ferences for representation of geometric forms; i. e., under states of elation a pictured human figure is larger in size than such a figure under states of depression.

Of more direct bearing on the present findings concerning the primitivization effect in terms of increase of size of body parts is the study, described earlier, which deals with the effect of boundary on perception of head size. In that study subjects were required to indicate the width of their own head under two conditions: (1) while E lightly touched S's temple, and (2) without E's touching S's temple. There it was found that head size decreased under light touch of the temples. The interpretation is based on the assumption that light touch of the temples articulates the boundary between head and environment, and in that way functions to decrease size. Taking the two experiments together, it can reasonably be argued that where boundary is strengthened, as in the above study, size of body parts decreases, and where boundary is lessened under conditions of LSD, size of body parts increases.

Summary

Under the influence of lysergic acid diethylamide (LSD-25), for both normals

and schizophrenics, there is a significant increase in the perceived size of one's own body and its parts, and no significant change in the perceived size of external objects. These findings are interpreted in terms of the assumption that LSD operates as a primitivizing agent, which is assumed to lessen the definiteness of the boundary of the body in relation to the surroundings.

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Reliability of the Methacholine (Mecholyl) Test

Variation in Results When Performed upon the Same Patient by Different Examiners

CAPT. JAMES W. MAAS (MC), U. S. A. F.

Introduction

In 1950 Funkenstein, Greenblatt, and Solomon¹ published their work with the epinephrine-methacholine (Mecholyl) test and its relation to prognosis with electroshock therapy (EST). In 1952² they further reported that prognosis could be predicted with the use of methacholine alone; i. e., those patients whose systolic blood pressure did not return to a basal level 25 minutes after injection with methacholine (a Type-6 curve) had a good prognosis with EST, as did those in whom the drug produced a chill and either relieved or precipitated severe anxiety. In further work^{3,4} these authors felt that the type of response was perhaps related to the secretion of epinephrine-like and arterenol-like substances—the former associated with “anger in” and failure to establish homeostasis, the latter with “anger out” and the return of the systolic blood pressure to at least the preexisting basal level. Further acceptance of the above assumption was brought about by the work of Elmadjian, Hope, and Freeman,⁵ who found a highly significant negative correlation between the rate of arterenol excretion in the urine and the log of the area representing the systolic blood pressure fall.

Much past work has indicated that when a drug is given, the resultant effect will frequently be a function of the chemical, the patient, the examiner, and the interaction of the three. An excellent example of this has been seen in the study of the efficacy of an antihypertensive agent by Shapiro, Myers, Reiser, and Ferris.⁶

All of the work done thus far has more or less indicated an assumption that the test results with methacholine are a function of the drug and the patient, with the observer a somewhat neutral quantity. Sloane, Lewis, and Slater⁷ make reference to varying results when the test was repeated by another person (in their study all testing was done by nurses), but they add: “This [difference in blood pressure responses to methacholine] was probably due to differences of technique more than to personality, although the latter undoubtedly played a role.”

Theoretically, one would expect the results of the methacholine test in some part to be a function of the examiner, since there is evidence, as mentioned earlier, to indicate that the direction of the anger will influence the type of blood pressure curve obtained. Thus, one might hypothesize an “anger-in” response with good prognostic results if the test were given by an authority figure, such as a physician and/or an armed forces officer. On the other hand, an “anger-out” response with poor prognostic test results might occur if the examiner were viewed as a nonthreatening figure, viz., a person who has nearly equal status with the patient. The following study was undertaken with this hypothesis in mind.

Methods

Twenty consecutive patients admitted to the male neuropsychiatric ward of this hospital were selected for this study. Only patients with asthma, signs of coronary or cerebral vascular arteriosclerosis, or evidence of disturbed physiology, as in the case of delirium tremens, were excluded from this study. After the systolic blood pressure had stabilized to readings every minute, within 4 mm. Hg of each other for five minutes, each

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Data on Individual Patients

Patient	Diagnosis	Examiner and Day of Test	Type of Curve	Anxiety or Chills	Time Required to Reach a Basal Systolic Blood Pressure Min.	Level of Basal Systolic Blood Pressure, Mm. Hg.
10 *	Schizophrenic reaction	{ Physician 2 Corpsman 1	Unfavorable Favorable	0 0	10 3	126 140
1 *	Anxiety reaction	{ Physician 2 Corpsman 1	Favorable Unfavorable	0 0	9 6	130 122
18 *	Neurotic depressive reaction	{ Physician 2 Corpsman 1	Unfavorable Favorable	0 0	6 0	126 132
7 *	Schizophrenic reaction, catatonic type	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	Anxiety 0	2 4	116 98
5 *	Psychophysiologic gastrointestinal reaction	{ Physician 2 Corpsman 1	Unfavorable Unfavorable	Chill Chill	4 4	136 130
12 *	Emotional instability reaction	{ Physician 2 Corpsman 2	Unfavorable Unfavorable	0 Anxiety	5 8	120 110
17 *	Anxiety reaction	{ Physician 2 Corpsman 1	Unfavorable Unfavorable	Anxiety 0	0 0	140 134
20 *	Neurotic depressive reaction	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	Chill Chill	1 2	120 128
15	Paranoid schizophrenic	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	9 0	150 142
3	Dissociative reaction	{ Physician 2 Corpsman 1	Unfavorable Unfavorable	0 0	3 11	110 106
8	Neurotic depressive reaction	{ Physician 2 Corpsman 1	Unfavorable Unfavorable	0 0	2 0	102 130
19	Psychogenic musculoskeletal reaction	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	2 0	124 120
13	Schizophrenic reaction	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	0 2	136 130
4	Schizoid personality	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	0 2	120 118
6	Psychophysiological G-I reaction	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	2 0	120 114
9	Paranoid schizophrenic	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	3 0	126 122
11	Anxiety reaction	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	0 8	118 112
2	Anxiety reaction	{ Physician 1 Corpsman 2	Unfavorable Unfavorable	0 0	1 0	136 134
14	Schizophrenic reaction, paranoid	{ Physician 2 Corpsman 1	Unfavorable Unfavorable	0 0	2 0	106 118
16	Schizophrenic reaction, not otherwise classifiable	{ Physician 2 Corpsman 1	Unfavorable Unfavorable	0 0	0 1	134 120

* Patient with favorable prognostic test results.

patient was given 10 mg. of methacholine chloride I. M.

All tests were performed between 8:00 a.m. and 9:30 a.m. Each patient was tested on both the third and the fourth day of his hospital admission. The initial tests were performed alternately by the physician, a captain, and the chief corpsman, a staff sergeant.* In this way, any consistent difference in results between the two tests, as an effect of the attitude toward retesting per se, could be ascertained.

* During the time the corpsman served as the examiner, the physician was immediately available in a room adjacent to the testing area. Since medical complications might possibly arise from the injection of methacholine, firm instructions

Although no definite attempts at role playing were attempted, the corpsman was instructed to be very friendly with the patients, and in general be "one of the troops," whereas the psychiatrist remained the physician and captain in charge of the ward. One day prior to the initial testing, all patients were interviewed by the physician for a period of one hour. After the test-retest days, they were seen for periods varying from 1 to 20 hours. None of the patients were given any medication 36 hours prior to testing.

were given the corpsman that, should he observe any suggestion of shock or respiratory distress, the physician was to be notified immediately. The nearness of the physician was not communicated to the patient.

Results

The basic data which are hereafter described are recorded in the accompanying Table.

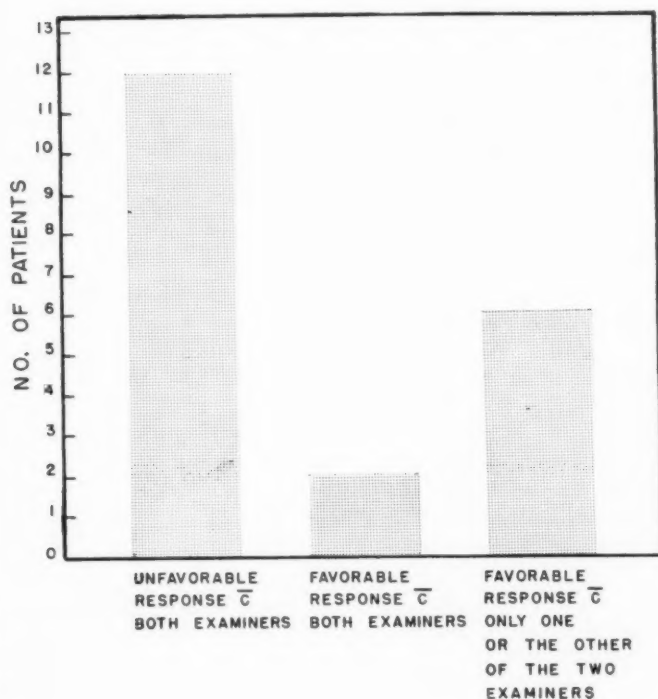
With 12 patients, both examiners received unfavorable prognostic responses.

Eight patients had responses of good prognostic import. Of these, six gave a favorable response with one or the other of the two examiners—three with the physician and three with the corpsman. (See the Figure and Table for further breakdown of these data.) Parenthetically, it is of interest to note that the type of response had no more than a chance relationship to the test day, that is, initial test and retest days.

In comparing the basal systolic blood pressures obtained by the two examiners on the test-retest days, it is noted that the physician obtained the higher reading in 10 cases and the technician in 5 cases. For the remaining five patients, both examiners ob-

tained readings which did not differ by more than 4 mm. Hg, and which were therefore considered to be equal. Despite this trend of the physician to note higher basal systolic pressures than the corpsman, in the group as a whole, the examiner who recorded a favorable prognostic result in all cases except one obtained the higher basal systolic blood pressure. This is pertinent to both Funkenstein's formulations of "anger-in" responses being associated with favorable prognostic test results and psychosomatic observations of chronic rage being etiologically important in hypertension.

A useful guide for predicting positive responses was the amount of time required for a basal systolic blood pressure to be established. For patients with Type-6 curves on either testing, this averaged 5.75 minutes; for those with either chills or anxiety, the average time was 3 minutes; for those with poor prognostic findings, the average time was 2 minutes. Although there were excep-



Responses of patients to methacholine (Mecho-lyl) classified prognostically.

tions, one was three times more frequently correct in predicting a favorable type response when it took four or more minutes for the blood pressure to stabilize at a basal level.

A concurrent check on recordings of blood pressure readings by the physician and the technician revealed no significant discrepancies; i.e., differences were all less than 4 mm. Hg.

Comment

The findings do not support the theoretical formulation that the physician would tend to obtain a greater number of favorable test results because of external signs and cues which promulgate an "anger-in" relationship, and/or that the corpsman would obtain a smaller number of favorable prognostic test results because of the patient's "anger-out" reaction. As a matter of fact, each examiner obtained a favorable response in three patients where the other did not. However, the individual patient's reaction to the examiners seemed to be quite important. A pertinent example of this is Patient 10 who, because of his ego structure and past experiences with psychiatrists, was able to form a very warm relationship with the physician. During the test, he was able to talk freely and made remarks such as: "When you're here, Doc, it's just like my Mom; I feel that I don't have to worry about anything."

When this same patient was tested by the technician, who was a corpsman staff sergeant (in the patient's eyes a rank which evoked a punitive stereotype), he was much more constrained and unable to express anger or, for that matter, any emotion. It is interesting to note that the patient's test with the technician was of a favorable type, while with the physician the results indicated an unfavorable prognosis. The original idea—that simply being a captain, etc., would evoke an "anger-in" response—is felt to be somewhat naïve. Patients in this series tended to react to the examiner in terms of their own ego structures. Thus, as in the case

mentioned above, the examiner's status as either a captain or a sergeant was meaningful to the patient, but in a way which was determined not by the external accouterments of the examiner, but by the manner in which the patient perceived him.

A similar situation was found by Grinker et al.,⁹ whose attempts to evoke stress in an interview were counteracted by the patient's tendency to perceive the examiner as one who was attempting to give assistance and not cause discomfort.

That the patients tended to react to the examiners according to their own ego structures is perhaps further borne out by the fact that, in all cases except one where there was a discrepancy between results, the examiner obtaining the favorable prognostic test also noted a higher basal systolic blood pressure, as would be expected with an "anger-in" response. This is particularly noteworthy when it is remembered that, for the series as a whole, the physician obtained higher basal systolic blood pressures, in the ratio of 2:1.

The marked difference between the two examinations in 6 of the 20 patients is most likely not a function of test repetition per se, since two previous papers^{7,8} have indicated a high reliability of results upon retesting by the same person. On the other hand, Sloane, Lewis, and Slater⁷ found the concordance of favorable prognostic ratings falling to 67% when the test was repeated by another examiner. It was probably important that all of the examiners in their series were nurses with whom, it would seem, the patients had had relatively little prior contact. In our series, each of the two test administrators knew the patients relatively well prior to testing, but in quite different capacities.

It has been observed that one is three times as often correct in predicting a favorable prognostic test when more than four minutes is required to obtain a basal systolic blood pressure. This observation poses some interesting problems and questions. One is tempted to think of the favorable test pat-

tern as being related to autonomic instability. There is some evidence^{10,11} that systolic blood pressure is a good indicator of autonomic response in general, but this is far from certain. In addition, Wenger and associates¹² have noted that work done on autonomic nervous system variables in a resting state are not necessarily related to what happens with stress, under which heading the methacholine test comes. Thus, any statements regarding increased time necessary to obtain a basal systolic blood pressure, autonomic instability, and favorable prognostic test results must for the present be speculative. However, a study has been begun in which the variable of time required to reach a basal systolic blood pressure is being used in an attempt to predict the test result.

Summary

Twenty male inpatients were given the methacholine (Mechohyl) test on two alternate days by a physician and a psychiatric corpsman.

Twelve patients had unfavorable prognostic test results for both examiners; two patients had favorable prognostic responses for both; three patients had a favorable prognostic response for the physician and not for the corpsman, and three patients had a favorable prognostic response for the corpsman but not for the physician.

It is felt that the disparate results obtained upon retesting by a different person are a function of the examiner and the way in which he is perceived by the patient.

The greater the time required to obtain a stable basal systolic blood pressure, the more likely one was to obtain a favorable prognostic test response.

It is felt that if the methacholine test is to be repeated, consistent results will not be obtainable with different examiners.

S/Sgt. Clifford A. Lowther gave technical assistance, and Drs. Louis Gottschalk, James Tichener, and Milton Kramer, of the University of Cincinnati, Department of Psychiatry, offered critical comments.

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Effects of a Tranquilizer (Reserpine) on Psychodynamic and Social Processes

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Most investigations of the tranquilizing drugs have placed emphasis on behavior and symptomatic aspects of a large number of patients but have left the psychodynamics of these drugs somewhat obscure.

We hope by intensive study of a few patients to gain more understanding of this problem. We chose four chronic regressed schizophrenics who had been under observation at the National Institute of Mental Health for nearly two years. They were all in intensive psychotherapy. Heroic efforts had been made to alter their regressive pattern. We had a high nurse-patient ratio, and all efforts were made to provide specialized and individual care. There was a strong belief on the part of the staff in the efficacy of milieu therapy and no lack of enthusiasm in working with the patients. These patients had shown relatively little progress during the two-year period. We felt they would be ideal candidates for a study of reserpine in the sense that the factors of enthusiasm and attention had been given an ample opportunity to have an effect. The ward had pinned its faith on psychological interventions, and the introduction of reserpine was greeted without any special enthusiasm. Two of these patients were so regressed that they lay in bed whenever permitted and became assaultive whenever their regressive pattern was interfered with. Two were incontinent. Three of them were feeding problems. One of them was mute, and another, while not mute, frequently responded to the staff with the rather stereotyped "Kiss my ———."

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We began the patients on a two-week period of control injections, after which they were given 5 mg. daily of reserpine intramuscularly. They received reserpine for a month; then had another two-week control period, and so on for a six-month period, at the conclusion of which the reserpine was stopped for a month. Daily ratings of behavior were made before, during, and after the study. Recordings were made of therapeutic interviews, and daily observations were made by the nurses. Neither therapists nor nurses working with these patients knew the dosage schedule.

In two patients sudden and dramatic changes were observed. Mrs. A. came to us at the age of 46. Although she had been sick only three years, she had already reached a very fixed regressive pattern. Before coming to us, she had had shock, insulin *Dauerschlaf*, and psychotherapy, without avail. Her illness had been precipitated when she, a widow of some 20 years, found that the man she was about to marry already had a wife. At the time of her admission she complained that she was a doll living in a world of puppets. She complained that the universe had been destroyed, and that she personally had destroyed it because she had eaten Christ and the Jews. She complained that she was dead and no longer existed. She referred to herself only in the third person. She spent all her time shredding her clothes and making tiny string dolls. The transfer to a new hospital brought no change in her regressive pattern; if possible, she regressed even further. She was incontinent of urine and feces. She refused to bathe or to dress; sometimes she had to be tube fed; at other times she ate raven-

ously. She became assaultive when any attempt were made to interfere with her regressive pattern. She was chronically agitated, pulling out her hair and picking at her face and nails until they bled. We attempted to establish a relationship with her by intensive nursing care, anticipating that this would ultimately lead to the establishment of a psychotherapeutic relationship. The nurses actually vied with one another to give her attention. This attention she soaked up, but it did not in any way alter her pattern of behavior. Her communications to the nurses were rambling and incoherent. A typical sample would run as follows: "Little man with blue eyes when he suggested—faint—stairs—end of gorgeous world—I should have suggested the Bible was for everybody; ages and ages ago, had no money, more education, more health. She never should have been led so far. I am not worth anything. You change all the time—just a piece of cardboard. Doll, doll, ass, you all fell through, floated through trash, this way and that. Now it is pretty late. A piece of shit, one pubic hair. Why did I ever give hands to anybody? I cannot have children. It was already criminal. Everybody started to invent Mrs. A. because she was a symbol of sickness." With her psychotherapist she was usually mute, except to snarl: "What do you want?," and to spit at him. She was frequently assaultive and tore the interview room apart. She took little interest in her surroundings, preferring to lie in bed. In her illness she was apparently making an effort to deny her loss and to protect herself against the pain of future intimacy.

Two days after reserpine was started, she was seen alternately crying and talking. She refused to have blood pressure taken, stating: "That's not my arm; that's a penis; there's no blood pressure in a penis; get that little thing with a bone out of here and stop wetting all over me." Two weeks after beginning reserpine, dramatic shifts occurred. The first evidence was when she got up and dressed and came to the Christ-

mas party, and even offered to help prepare sandwiches. This was the first time she had ever taken any interest in anyone else on the ward. When cautioned about eating all the sandwiches, she laughed and said: "Well, I might eat just one or two." Ordinarily she would have wolfed the lot of them. She began going out to shop for attractive clothes and visiting old friends. She now came eagerly to her psychotherapy hours and also went on long walks with her therapist. She began to speak of herself in the first person. The primary process was replaced by the secondary process in her thinking. Instead of complaining about her delusions, she complained that she was old and sick and did not have much of a future left. Often she appeared visibly depressed. Yet she participated in group therapy and became the group humorist.

B. was a 25-year-old schizophrenic who had an acute break while in the service. He was an only child of anxious, domineering parents, who ran his life and permitted him no relationship outside the family. Thus he was completely unprepared for the life in the Army. He developed many persecutory ideas and went into an acute panic. He received electroshock, became confused and disorganized, and escaped from the service hospital. He returned voluntarily, apparently having given up the struggle, as he then retreated into a shell, from which he did not emerge. Although he had been sick only a year, he established a fairly regressed pattern. After his admission to the Clinical Center, he regressed even further. He did not talk. Whenever he was permitted, he lay on his bed covering himself with a newspaper or blanket, or even with the mattress, limp as a meal sack. He became assaultive if any attempt was made to interfere with his regressed behavior. His pattern of alternating withdrawal and assaultiveness made everyone uncomfortable in dealing with him. He successfully resisted intensive and persistent efforts at intervention. The only sign of emotion he evinced was to laugh when he struck at

people and they ducked. He ate sparingly and yet often hoarded food in his bureau drawers. He resisted shaving and bathing. Four days after reserpine was started, he astounded everyone by coming to the nursing station and asking: "Can I go downstairs to the cafeteria and get something to eat?" He went to the cafeteria and ordered blueberry cobbler, coffee, and ice cream. After this he ate at the table with the others at mealtime. After five days of reserpine he went out on a shopping expedition and then went to see a former girl friend, and even visited his parents. After leaving his parents, he again became silent and withdrawn. He continued to go out on visits. He moved in with a roommate. He visited with old friends and talked over old times. He shaved himself and looked after his appearance. He went to movies and even to bars. On the 10th day of reserpine his nurse noted: "1. He was able to talk with ease. 2. He was more of a gentleman: He held the door open for me. 3. He responded more readily and spontaneously to my remarks and questions. 4. He inquired about other patients on the ward."

A third patient showed similar changes but not of the dramatic quality of the first two. C. was a 36-year-old single man who had been hospitalized for only two years but who had apparently been sick for a very long time. His mother had died when he was 6 years old. His father had abandoned him to the care of grandparents, who were contemptuous of both him and his father. He grew up lonely and isolated and uninspired. He had been arrested for pinching women's bottoms, which arrest precipitated his hospitalization. He explained that the women had been telling him to "take him" and that he could feel their passion streaming into him, even through the walls of his room. In the hospital he became first agitated by the presence of the nurses. He then retreated to his room whenever possible, lying in bed and masturbating, when he was not writing letters to General Marshall. He found a roommate intolerable,

attempting when he could to sleep in the television room or the bathroom. Occasionally he was regressed and indifferent, sometimes assaultive. He made little progress in dealing with his problems in therapy.

Reserpine initially increased his sexual preoccupations and strivings. He complained the nurses were inside his body. He became intensely agitated and assaultive. Thereafter his aggressiveness subsided. He became comfortable. His psychotic content, his delusions and hallucinations, decreased. Instead he had many dreams. One such dream was as follows: "There's a stream or something surrounding a city that's practically empty, and there's a bridge that you try to get across; and then after you get across, you're nowhere. It's just a big, like a deserted place, like a coliseum or something. It's a hell of a spooky place, big slabs of stone and rock all over the place." This dream illustrates the intense isolation, impotence, and desolation of his existence. He did not, however, show any interest in trying to understand these dreams. Nor did he show any interest in doing something about the isolation and dreariness of his existence. He preferred sleeping to activity.

The fourth patient was made worse by reserpine. D. was a 36-year-old woman who had been sick for 17 years and who had been institutionalized for 15 years. Her illness had had an acute onset while she was in college. She had been neglected by her mother, who had been so preoccupied in reading novels that she forgot to feed her. She was her father's favorite, and she developed an intense attachment to him. While still in school, she had a real or imagined affair with her employer, and after this she became acutely disturbed and assaultive and had to be taken to the hospital by the police. She improved for a while, and then after her mother's death, in the second year of her hospitalization, she became progressively deteriorated, until she had to be placed on the most regressed ward in the state hospital. Despite the chronicity of her

illness, she was still very attractive and retained considerable appeal for the staff both at the state hospital and at our hospital. She appeared silly, giddy, flighty, openly demonstrative, and affectionate, although she would occasionally strike at people. Her speech was incoherent. She would repeat: "Do it; do it; hearts and hearts." When asked if she heard voices, she would reply: "Yes, they say, 'see your dentist twice a year and brush your teeth twice a day.'" She showed little response to psychotherapy, usually refusing to see her therapist.

Soon after getting reserpine, she became more disturbed, assaultive, and aggressive. She then developed Parkinson-like symptoms of rigidity and tremor. She drooled and could barely hold a cigarette. She now remained in her therapy hours, but apparently only because she was immobilized. No change of speech content or attitude was observed. The staff was extremely disturbed. D. was their favorite patient. Seeing what appeared to be miraculous changes in the other patients, they had begun to nurture high hopes for her and were bitterly disappointed that she, of all the patients, failed to respond favorably. They were made very uncomfortable by her induced helplessness.

The most prominent change in the patients who improved was an increased friendliness and a considerable concern for the feelings of other people. Thus, of Mrs. A., who formerly spat, bit, and scratched in response to any effort at closeness, the nurse reported the following interchange: "She was rather lucid as she met me in the corridor. She kissed me three times on the cheek, hugged me, and told me: 'I hear you are leaving. You are a nice person and very good looking. I shouldn't tell you this but they are planning a party to celebrate on your last day.' I thanked Mrs. A. with a lump in my throat."

Mrs. A. came to her therapy hour one day and, angered by a remark of the therapist, threw an empty coffee cup at him.

(Before reserpine she had thrown chairs when she was angry.) She left the hour in a huff, but returned a few minutes later, carefully picked up the cup, and replaced it and apologized. The patients also eagerly sought out old friends, but toward strangers they remained aloof and diffident. Mrs. A. was gracious and cordial to strangers when she was in the company of the therapist. But if a chance stranger came on the ward, she would revert to her former pattern of telling him to kiss her —.

These patients did not have a lessened titer of aggression, but it was more discrete, better controlled, and expressed in more acceptable manner. Mrs. A. stopped spitting at the therapist after receiving reserpine. This did not seem to represent a decrease in her aggression but indicated a greater awareness and tolerance for friendly feelings, as well as a concern for the feelings of others, so that she expressed her aggressions in other ways, such as telling her therapist that his shoes were filthy and that he wasn't much good as a therapist. Other impulses were also better controlled and channeled. Instead of masturbating, Mrs. A. engaged in more acceptable activity, such as dancing and going for walks. With reserpine the patients appeared more able to tolerate delays and frustrations. Delay mechanisms were enhanced. Mrs. A., who formerly would have gobbled all the food on the table, now nibbled daintily on a sandwich. She, who formerly would have struck someone who frustrated her, now made visible efforts at self-control.

The patients had vivid dreams. These dreams seemed to be characterized by the appearance of what had formerly been expressed as delusion. Mrs. A. had the following dream: "I ate 50,000 rubles, which invoked the disfavor of all my acquaintances, which left me unable to bear children." In her delusions she had previously stated that she had destroyed the universe and turned everything to shit by eating too much. This delusion originally stemmed in part from her having performed

fellatio with her lover. The affective component of this delusion could still be found in her complaint that the reserpine was giving her too big an appetite, that she was gaining too much weight, and that her clothes no longer fitted her.

The effects on psychotherapy were somewhat ambiguous. B., who had been mute, now talked with everyone but his therapist. C. often slept during his therapy hours. Mrs. A., who had been unwilling to talk to her therapist, now became quite friendly and garrulous. She took long walks with him. She commented on how real everything had become. She admired the trees and the birds and recalled how she had used to enjoy all these things. One day she saw a rabbit out on the grounds and returned to the ward with tears in her eyes. "That bunny was so beautiful. It was so real." Occasionally she would say: "Look, I'm old, and tired and sick. What does life hold in it for me?" But most of the time she avoided carefully any of her problems. If they were raised during her therapy hour, she would get angry and leave or ignore them, or cover them up as effectively with her amiable speech as she had in the past with her hostile silence. She said the reserpine was for the doctor's benefit and wanted to know when it could be stopped.

The therapeutic situation was improved in that both patient and doctor were more comfortable and the mutual anxiety was decreased. It transformed a disjunctive hour that both dreaded into one that both welcomed. The content of speech was less concerned with delusions and more with daily living. However, the psychotherapeutic situation was improved only in the sense that all social and interpersonal relations were better. In the sense of therapy as a collaborative investigation into the patients' difficulties in living, psychotherapy was not facilitated. All the patients avoided sensitive areas as effectively as they had before reserpine. Their improved functioning seemed predicated on a successful denial

of their problems and avoidance of their difficulties.

The pattern of staff reactions to the administration of reserpine is illustrated by a quotation from one of the nurses: "You hate to think it's a drug. But it's wonderful to have B. come out of his cocoon. It makes you less anxious. Before he was so tense and anxious; it was bound to make you anxious. It enables them to tolerate living to a point where you can get to them. But when you put out a lot of effort, you hate to think it's reserpine. Reserpine alone wouldn't do any good." A therapist who did not believe in drugs scoffed: "He was about to make the move anyhow."

We are faced with the problem of why the patients hit a plateau beyond which they did not continue to improve. This may in part have been habituation to the drug, but with two patients partial relapse occurred dramatically. All four patients became adjusted to the pattern of daily living on the ward, but none appeared well equipped for the problems of the outside world. Mrs. A. showed a prompt reversal in her behavior after reestablishing contact with her family. After five months on reserpine she had improved to the point where she could call up her brother in Paris. (She had had many problems with this brother, and he had been quite critical of her affair.) She spoke rationally to him for about 10 minutes. Immediately afterward she was back in bed. She refused to see her therapist, saying he was all shit. She denied having a brother. She remained in bed, and the nurse's notes state: "The old Mrs. A. could be seen clearly. Back on the old theme of 'nothing is real and what is the use?' Really depressed and hostile. Called me a big-nosed bitch."

This illustrated that the reserpine had not rendered her immune to environmental stress. Apparently reserpine failed to relieve the basic conflicts which had precipitated her illness. The persistence of these conflicts is illustrated by the following: Mrs. A.'s illness had been precipitated

when she was deserted by her lover. When she emerged from her psychosis, she began to demand that the therapist make arrangements for her to see the lover again. Following this she had the following dream: "Someone was committing suicide. I had been married three times, instead of two. And that was a marriage when I came back and he wanted me to stay with him. At the same time he had already been attached to the other woman, and besides he had a child." This dream is an expression of the same conflict. She had wanted her lover to marry her, but he had refused because he was already married. Getting well involves the acceptance of the loss of her lover. She must endure the pain and mourning of giving him up. But she is unable to do this and continues to cling to him. She will not talk about him in therapy. Getting well also involves a massive number of readjustments. When she was well, she was still attractive. Now she is old, broken, and ugly. Every time she goes out, she sees pretty things she used to enjoy—clothes; good times. It seems an insuperable job to make anything of her life now. And she gives up; she cannot make the effort.

B. furnishes a somewhat parallel example. As B. improved, his family moved in to take over his life and run it according to their established pattern. It must be noted that B. participated in this, actively seeking them out and visiting them whenever he could. B. had been within the confines of the hospital for almost a year; yet when he began going out on his own, the family complained that he was spending too much money. (It was his money.) After this he stopped his trips. He had isolated himself for over a year; yet when he moved in with another patient, the family protested about the possibility of homosexual relations. B. was unable to protest directly. One day the entire family visited the Jefferson Memorial and B. read the inscription about the priceless heritage of freedom and gave a bitter laugh. He has not continued to improve since this. Apparently, getting

well means returning to the family, where no freedom is allowed. Unless he can work out his relations with the family in therapy, there is no hope of freedom for him. Possibly this is too painful a prospect. He can only retreat.

Our rating scales showed no significant differences between behavior during the control periods and that during the reserpine periods, although they showed a significant difference between the before-reserpine and the after-reserpine periods. From this we conclude that the two-week control period was insufficient for the reserpine effect to wear off. A month after the conclusion of the experiment the patients were put back on reserpine. Two of the patients asked for it themselves for help in relieving their tension. One therapist asked for it (for the patient) because he could not bear the patient without it. This time similar, though less dramatic, results were observed.

Let us enumerate the observations which are to be accounted for in a dynamic formulation of the action of reserpine.

1. The evidences of the patient's anxiety are decreased. This decreases the anxiety of the staff and makes the world a more comfortable place for the patient.
2. The patients are more friendly, make more contacts with the external world, and are less preoccupied with themselves.
3. The patients show greater self-control and social conformity.
4. Depression is not an uncommon feature.
5. The patients' thinking becomes less dominated by the primary process. The secondary process again comes into play.
6. The delusional material becomes less prominent in waking life and now makes its appearance in the dream.
7. Psychotherapy is a more agreeable collaboration, but one in which sensitive topics are still avoided.
8. The drug effect is reversible not only when it is discontinued but when external

pressures place the patient in a disturbing situation.

The effects of reserpine can be usefully described in terms of structural changes in the ego. We are postulating that it is as though reserpine increases the sensory or protective barrier of the ego. According to Fenichel's¹ interpretation of Freud:

As long as intensive stimuli from the outside world flood the organism, the organism experiences this passively. The construction of a perception apparatus, coinciding with an apparatus protecting against too intense stimuli, brings about a change from passivity to activity.

Because of this stimulus barrier, only a fraction of the stimuli reaching the normal person become perceptions. In a psychotic patient the protective barrier of the ego is disturbed; he is overwhelmed by stimuli, and his discriminatory powers are lost. With this disturbance of the protective barrier, the ego becomes flooded with id impulses; reality testing is lost, and the primary process holds sway.

Upon the administration of reserpine the protective barrier is strengthened, so that the patient is no longer flooded with stimuli and id impulses and regains some of his former discriminatory power. Aggressive impulses and others, which previously could not be neutralized by the poorly differentiated ego, are now better controlled. The anxiety experienced is decreased, and with improved ego functioning there is a reduction in transference distortions. The patient, as it happened with Mrs. A., may now see the doctor as doctor rather than as a Negro criminal.

The not infrequent appearance of depression may, in addition to the physiologic depression of function which reserpine seems to induce, have a twofold psychodynamic origin. With the strengthening of the repressive barrier of the ego there is a reinforcing of the condemning and punitive superego attitude, which lead to conforming

behavior and sometimes to depression. Also, as Bibring² has suggested, depression may arise from the prehension of helplessness. The patient, because of his increased discriminatory power, becomes more aware of the actuality of his helpless position. Reserpine makes the patient dependent on the powerful figure of the physician, who, by prescribing a pill, is able to control and dictate his conformity.

In accord with this reasoning is the finding that psychotherapy is not facilitated. The action of reserpine, which leads to repression of conflicts, is antithetical to psychotherapy, where the aim is the reintegration of conflicts within the structure of the ego.

Summary and Conclusions

Reserpine has a dramatic effect even in a therapeutic milieu.

Reserpine affects favorably not only the patient but the patient-staff interaction.

Reserpine administration leads to a strengthening of the perceptual and repressive barriers of the ego.

Reserpine within this sample did not facilitate psychotherapy.

Reserpine did not have an effect which lasted after reserpine was discontinued.

Unfavorable environmental stress can reverse the favorable effect of reserpine.

National Institute of Mental Health (14).

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Chemotherapeutic Trials in Psychosis

II. Design and Conduct of a Trial of Raunormine Versus Reserpine and Phenobarbital in Chronic Schizophrenia

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The introduction of new and allegedly improved physical and pharmacological treatments in psychiatry is proceeding at a remarkable rate. Many reports of such "treatments" are so deficient in one or more of the fundamental elements of experimental design or reporting procedures as to be valueless, and by their very publication compound confusion. This has led to several major conferences within the past year devoted to questions of designing, conducting, and reporting on new therapies.^{1,2}

The present investigation was started in 1954 with the intent to compare reserpine with 11-desmethoxyreserpine (Raunormine), which is obtainable from plants growing in the Western Hemisphere.³ At the time there were many laudatory reports on the value of reserpine in treatment of hospitalized schizophrenic patients, but there were questions unanswered as to duration of an adequate trial and of effective dosage. While it was known at the start of this work that Raunormine possessed properties closely resembling, if not identical with, those of reserpine,^{4,7} there was no certainty that as chemopsychiatric agents their optimal dosage would coincide. The possibility could not be excluded that their psychic effects might differ qualitatively. To investigate these matters, the present experi-

ment was designed. It will be seen that this study covers some considerations not fully developed in the recommendations of the latest conference on evaluation of chemopsychiatric agents.²

Materials and Methods

Treatment Setting.—Chronic hospitalized schizophrenic subjects chosen were distributed over 13 wards at the Central Islip State Hospital. These wards are all overcrowded to some extent; some are older structures; some are of new, modern brick design. The extensive use of chlorpromazine and of reserpine had been introduced in 1954, with consequent improvement in the entire milieu. The ratio of patients to personnel was such that little individual attention could be given to patients. Nonetheless, in this present study there was such over-all cooperation, interest, and even enthusiasm on the part of all personnel at all levels that it could fairly be said to equal that available in all but the most expensive private or university hospitals.

Subjects.—For the study, 150 women and 150 men between the ages of 18 and 45 were selected by their ward physicians. About 30% had had previous trials of chlorpromazine or small doses of reserpine for short periods of time. None were expected to leave the hospital in the four months between the time of their selection and the actual start of the medication. None were known to have any physical disease, epilepsy, or organic brain pathology. About 20% had shown improvement within the previous year under one therapy or another. In the year since this trial terminated many have improved under a regimen, introduced early in 1957, directed toward the "open-hospital" policy.

Medication.—Inasmuch as the question was unanswered in 1954 as to what influence of reserpine might be attributable to sedation alone, and since the design of our trial called for a placebo, phenobarbital was selected to serve both needs. Four dosage levels of reserpine and of Raunormine,

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respectively, were established on the basis of previous reports, to cover the entire range from that thought to be a minimally effective dosage to that which would produce such side-reactions as to limit its value. In the opening phases of the work we were led to believe that four months would be an adequate trial duration.

The dosages for the first period of eight weeks were 0.3, 0.9, 2.7, and 8.4 mg. per day. For the second period of eight weeks we began by doubling the doses, but found that this produced disabling paralysis agitans and soporific states. Therefore the last seven weeks were passed with doses of 0.45, 1.35, 4.05, and 12.6 mg. per day. To each set of eight subjects receiving the above medication, two received phenobarbital, at first 0.2 gm., and later 0.3 gm., per day. All medication was made up in a slightly acidified cherry syrup with 20% alcohol. This was exceptionally well taken by the patients, and administration in this form obviated many of the difficulties attendant upon the use of pills.

The bottles containing the drugs were labeled "Rauwolfia Compound," with designations C through L. The identity of the contents remained secret until the trial results were all analyzed.

As there were 10 bottles for the 10 subjects in each set, patients on wards were chosen in groups of 10 and randomized by assigning rank order according to their hospital admission numbers, which were then scrambled according to tables of random numbers.

Testing Procedures.—Seven psychologists, candidates for the Ph.D. degree at Adelphi College, who had had prior experience with state hospital patients, were trained in the use of the Lorr Multidimensional Rating Scale for Rating Psychiatric Patients.⁸ The training was done in group sessions, in a nonauthoritarian setting. At the conclusion of the training, 14 patients were rated by each psychologist and one of us (W. J. T.) on the basis of interviews conducted before the rest of the group. The data so obtained demonstrated the interreliability of the raters.*

* Under each factor, A, C, E, F, G, J, and K, the ratings given by eight observers were ranked from 1 to n , where n is the number of patients. For each patient the sum of the ranks was obtained. A coefficient of concordance was calculated from the formula $W' = \frac{12S}{m^2(n^2 - n)}$, where W' is the coefficient of concordance, S , is the sum of squares of deviations of the rank totals from the mean total, m is the number of observers, and n is the number of patients.¹⁰ The following values were obtained:

Factor	A	C	E	F	G	J	K
W'	83.04	81.60	39.76	87.89	89.84	75.86	86.64

The maximum value obtainable is 100, representing

Results

All the data were subjected to statistical evaluation. At the end of the first two months there was no change of statistical significance (at 5% level) between the pre- and post-treatment evaluations, nor did we who rated and saw the patients observe that there was much change. Slight movements toward the normal did occur in the Rauwolfia subjects, and away from the normal in those taking phenobarbital; but these were not significant. It was clear, however, that the patients receiving various levels of medication were comparable members of the same population at both testing periods; this was further proof that our methods of selection and randomization had achieved their goals.

The data at the end of the four-month period were subjected to a more thorough scrutiny and evaluation. We were at first pleased to learn that four subjects on reserpine had left the hospital. From discussions with the ward physicians and personnel we learned, however, that one of these had been approved for convalescent status prior to medication; two were sent out partly under family pressure, and all four left within the first month of reserpine therapy. None was thought to have benefited from the treatment, unless it be that the period of tension prior to release was gone through more calmly than usual.

At the conclusion of the trial consultation was held and the statisticians' analyses were reported and reviewed. We quote a portion of the report on the four-month evaluation.

"The data were received by us in the form of booklets giving the grades on 63 characteristics. For each patient there was a booklet with initial ratings, another with ratings after two months, and a third with

perfect agreement. The values were quite satisfactory, except in the case of Factor E. This factor concerns items relating to manic-depressive manifestations. The lack of agreement here actually reflects the adequacy of selection of patients as schizophrenic, for it really means that the patients were so alike that high correlation of observers could not manifest itself.

ratings after four months. There were about 55 patients who received phenobarbital and who served as controls. Each treatment group contained approximately 30 patients.

"The 63 readings were combined according to directions in TB 10-507,⁸ to furnish 11 readings on the following characteristics:

	Norm
A. Retarded depression <i>vs.</i> manic excitement	17
B. Compliance <i>vs.</i> resistiveness	4
C. Paranoid projection	3
D. Activity level	13.5
E. Melancholy agitation	13.5
F. Perceptual distortion	5
G. Motor disturbances	9
H. Submissiveness <i>vs.</i> belligerence	11
I. Withdrawal	15
J. Self-deprecation <i>vs.</i> grandiose expansiveness	9
K. Conceptual disorganization	7

"For each of these characters there is a score representing a presumed normal person, as shown in the third column. It appeared that a suitable criterion of effectiveness of the treatments might be obtained from the change in score after a period of treatment, movement toward the norm indicating effectiveness, regardless of whether the initial reading was above or below the norm. Such movements could be compared with the movements of the control patients.

"By plotting these movements, it was discovered that the extent of the movements was correlated with the initial distance from the norm. Patients initially far from the norm were more likely to show a larger movement toward the norm than those who were initially closer to the norm.

"Furthermore, those subjects who were originally close to the norm cannot be ex-

pected to furnish much information about the success of the treatments; in fact, such persons only serve to dilute the data and to obscure treatment effects which might exist.

"Therefore comparisons were made using only the half of the sample whose members were most distant from the norm initially. While this decreases the size of the sample, it increases the efficiency of the comparisons.

"In order to obtain a statistical test of the significance of the difference between treated and control patients, the Wilcoxon rank test was used, as described by Siegel.⁹

"A statistical test of significance was performed by attaching rank members 1 to 35 to the distances from the norm of both groups together. Report R132/S86 of the Mathematical Centre, Amsterdam, gives tables obtained if both groups are drawn from the same population. For Factor G, the rank total for the control group is 496.5 and for the reserpine group 133.5. The expected values are 450 and 180, respectively. The probability of a deviation of 46.5 is 0.045, and therefore it may be concluded that this deviation is significant at the 5% level. In a similar manner, the data on Factor G, Raunormine high dose, may be shown to exhibit a significant effect of the treatment, the probability in this case being 0.021.

"When the methods described above were applied to Factors A through K after four months' treatment, results significant at 5% or better were obtained only on Factors B, G, and K" (Table 1).

As can be seen in Table 1, the low doses of reserpine (0.45-1.35 mg. per day) had no significant effect. Higher doses of reser-

TABLE 1.—Probability of Significance of Difference* Between Treated Patients (T) and Control Patients (C) for Factors B, G, and K of the Lorr Rating Scale

Factor	No. of Patients	Reserpine †		Raunormine †		No. of Patients
		High Dose	Low Dose	High Dose	Low Dose	
B	T 28					T 21
Compliance <i>vs.</i> resistiveness	C 26	0.018	Not significant	0.055	0.043	C 26
G	T 24					T 14
Motor disturbance	C 25	0.023	Not significant	0.040	0.042	C 25
K	T 20					T 20
Conceptual disorganization	C 20	0.022	Not significant	0.022	0.005	C 20

* Wilcoxon Rank Test.⁹

† High dose: 12.6 and 4.05 mg/day; low dose: 1.3 and 0.45 mg/day.

TABLE 2.—Average Movements, at Four Months, Expressed in Percentages of Possible Movements Toward the Norm of Those Patients' Ratings Which Were Originally Farthest from the Norm

Alkaloid Concentration, Mg./Ml.	Factor	0.01		0.03		0.09		0.27	
		Control	Rau.*	Res.*	Rau.	Res.	Rau.	Res.	Rau.
B	Compliance <i>vs.</i> resistiveness	9	36	0	28	22	38	37	18
G	Motor disturbance	3	42	13	14	18	38	35	39
K	Conceptual disorganization	5	9	10	28	15	13	14	18

* Dosage: 10 ml. t. i. d. for eight weeks, followed by 15 ml. t. i. d. for eight weeks.

pine (4.05-12.6 mg. per day) correlated with improvement only in compliance, motor activity, and conceptual organization. These three items were also the only ones which improved under Raunormine, but with this drug significant changes occurred at the lower, as well as at the higher, doses.

As another measure of the effects observed, we calculated the average distance of the patients from the norm initially and after four months' treatment. The movement toward the norm was then expressed as a percentage of the possible movement toward the norm. The results of the calculation are presented in Table 2. As can be seen, even in those factors which exhibited improvement at the 5% level of confidence, using only those patients originally farthest from the norm (whose movements had been shown to be greatest), in no instance did the average movement of a patient set move more than 47% of the way toward the norm. Our unmeasured evaluation of the individual patients whom we saw during the entire period confirmed the evaluations of our psychologists and statisticians: Patients were less agitated, less resistive, and somewhat better able to communicate in a meaningful manner, but there were many (within any one group) in whom no change had occurred.

In a further effort to understand the action of these agents, the records of those patients who had shown the greatest movement toward the norm were searched and the patients reinterviewed. We could find nothing in common among this group of patients "most improved" under reserpine or Raunormine that could distinguish them

from those who had shown little or no improvement.

Comment

When the present study was undertaken, we had certain information regarding reserpine. We knew that its action was not as well defined as some investigators had at first led us to believe. Its activity indicated that it would not be possible to deal with it as one might deal with a study of insulin in diabetes or of liver in pernicious anemia. There was no all-or-none response to be expected. Because of this, it was felt that a significant study would require the largest number of subjects we could accurately test. On the other hand, considerations of cost, of time available, and of the number of testers we could train and use limited the number of subjects we could employ. Were we to study the acute schizophrenics, whose "spontaneous" recovery rates are high and unpredictable, we would require a very much larger number of subjects than would be required for study of the chronic schizophrenic population. We were conscious of the possibility that it is perhaps just with acute schizophrenics that reserpine may find its maximal and real value. On the other hand, the situation of a large number of chronic schizophrenics is such that they have no primary or secondary gain to be achieved in recovery. Most of them still have no one and no place to go to. Their ability to respond to any therapy might be limited also by other factors, the equivalent, say, of scarring. However, recovery had already been promised by those whose early reports on schizophrenia had introduced reserpine into the psychiatric armamen-

tarium. The need for a treatment of chronic schizophrenia is most urgent, and no hope should be unexplored. In view of this situation, a study of chronic schizophrenics was both justified and essential.

Preliminary studies with Raunormine and reserpine were made for several months on 10 pairs of subjects. These convinced us that the differences between the two agents would be so small as to require a large sample population, and that 20 subjects per dosage level would be minimum. With a certainty that many of the patients chosen would not complete the trial, the number of subjects was increased to the maximum (30), which could be tested by the seven psychologists we had found who could carry out the work.

In our work there were fewer limitations than are generally imposed upon investigators; yet we had to limit the amount of time an examiner spent in evaluating one subject. We would make apology for the use of the Lorr Scale, for several reasons. First, a number of items relevant to the behavior of the patient are not included as items in the factor analysis. Second, the test is set up against a hypothetical normal person, a situation which offers three difficulties: (a) No one can decide how wide is the range of behavior in the "normal" person; (b) we have absolutely no information as to how a "normal" person would behave and think if he were in a hospital ward; (c) the hypothetical normal of the scale is often approached in actual testing with patients whose psychosis is still so frank as to require institutional care, and the few items which may be critical are given the same weight as items which are irrelevant to this particular subject. Nonetheless, this test was used because it covered the majority of items of interest better than any other single test that can be completed in one hour. It derives information both from the brief interview by a skilled psychologist and from the longer-term knowledge of an attendant or nurse. When it is used by a group of examiners under

the conditions described, the data are valuable for comparison within the limits of this set of conditions. For our purposes, then, the Lorr Scale was highly suitable.

However, it was necessary to take into account the personal involvement of the examiners with the subjects. As is well known, the very helplessness of the schizophrenics induces in those who deal with them immediate responses of various kinds and degree. This reaction we met with from the very start; examiners at once began to assume roles of therapists, or protectors, or siblings. For this reason frequent consultation between one of us (W. J. T.) and the examiners was held, and such effort was made as was feasible to relieve the examiners of the need to assume another role by the psychiatrist's offering as it were, to assume the burden. It is thought that some such action is essential in work with psychotic subjects. Report of a therapeutic success should be accepted with great caution when it comes from the person who deals directly with the patient.

Finally, a comment on the results of our endeavors is in order: Since this work started, evidence has been accumulating that reserpine has little effect in chronic schizophrenics at any dosage level.¹¹⁻¹⁴ What action does take place occurs over a period of time at doses almost always above 4 mg. a day. The original claims have not been substantiated, at least with the kind of subjects with which this report deals.

Summary

There is described and discussed the design, conduct, and results of a chemotherapeutic trial, wherein two therapeutic agents (11-desmethoxyreserpine [Raunormine] and reserpine) were compared with one another against an "active placebo" (phenobarbital), which possesses some of the physiological actions of the compounds under trial. Four dosage levels of each trial compound were employed. In chronic schizophrenics reserpine was ineffective below 4 mg. per day. Reserpine at 4-12 mg. per day was equaled

by Raunormine, both at low doses (0.45-1.35 mg. per day) and at the level of 4-12 mg. per day. Neither compound exerted any markedly beneficial effects.

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Correction

Through error the name of Dr. Percival Bailey was appended to the review of the book "Les Mécanismes cérébraux de la prise de conscience," by P. Chauchard (December, 1957, issue, p. 666). This review was written by Dr. Louis Berlin.

Studies in Psychophysiology of Dreams

I. Experimental Evocation of Sequential Dream Episodes

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Dreams have been a source of interest to psychiatrists and psychologists for many years. Their incidence, structure, and function have been studied from many different theoretical positions. To Freud the dream was essentially a disguised wish fulfillment which functioned to preserve sleep. Freud recognized that multiple dreams may occur on a given night and said:

In interpreting dreams consisting of several main sections, or in general, dreams occurring during the same night, the possibility should not be overlooked that separate and successive dreams of this kind may have the same meaning, and may be giving expression to the same impulse in different material. If so, the first of these homologous dreams to occur is often the more distorted and timid, while the succeeding one will be more confident and distinct.⁹

Alexander pointed out:

Often, however, the relation between pairs of dreams is still closer: not only is the content connected but there is also a dynamic or, more correctly, an economic connection. A certain dynamic relation between pairs or series of dreams which express the same wish is nearly always present.¹⁰

Many have felt that dreaming occurs more frequently during the night than reports of dream experience would lead one to believe. However, in order to elucidate the exact interrelationships of sequential dreams, one requires a record of the complete content of a night's dreams. Records of this type also may facilitate understanding of the significance of dreaming as a psychological and a physiological phenomenon.

The researches of Aserinsky and Kleitman,² Dement,³ and Dement and Kleitman^{4,5} have demonstrated that continuous monitoring of electrical recordings of eye movements and brain waves during sleep

allows an accurate determination of the occurrence of dreaming. These investigations have culminated in the demonstration⁵ that the physiological correlates of visual dreaming consist of low-voltage, nonspindling brain wave patterns associated with the presence of rapid eye movements (Fig. 1). Thus, since a period of dreaming can be accurately isolated from nondreaming periods of sleep, the possibility of obtaining detailed dream material at the time of its occurrence becomes feasible. How best to obtain such dream material with a minimum loss of content remains a major methodological problem for any research into the psychological elements of the dream.

Dement and Kleitman⁴ were able to obtain an 80% dream recall when they awakened their subjects (Ss) during the course of the dream. Awakenings were usually made 5-20 minutes after the dream had started. The disadvantage of using this method for obtaining dream material when investigating psychological variables, as pointed out by Dement and Wolpert,⁷ is that an unknown amount of the dream is lost by such interruption. To be certain that the dream has progressed to an unambiguous end, on the other hand, requires the experimenter (E) to defer awakening S until the appearance of the spindling pattern, associated with a deeper, nondreaming sleep; and by the time such a pattern has appeared, dream recall drops precipitously. Thus E is faced with the dilemma of awakening S either at times permitting maximum recall of incomplete dreams, or at times permitting minimum recall of completed dreams.

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An alternative is suggested by Dement and Wolpert's observation⁶ that gross body movements interrupting dreams signal a change in the dream activity. By awakening S during gross body movements it should be possible to isolate complete dream episodes, if not complete dreams, at their apparent natural termination. However, the fact that S is moving at the time the awakening stimulus is applied may diminish dream recall. In order to assess the usefulness of this method for obtaining dream episodes, a comparative study was made of the amount of dream recall obtainable using different awakening procedures.

Method

Ten men were studied for a total of 51 nights of experimental sleep. One subject was studied for 20 nights; a second, for 12 nights, and the remaining eight, less intensively.

In each case S was asked to report to the laboratory shortly before his usual bedtime. The

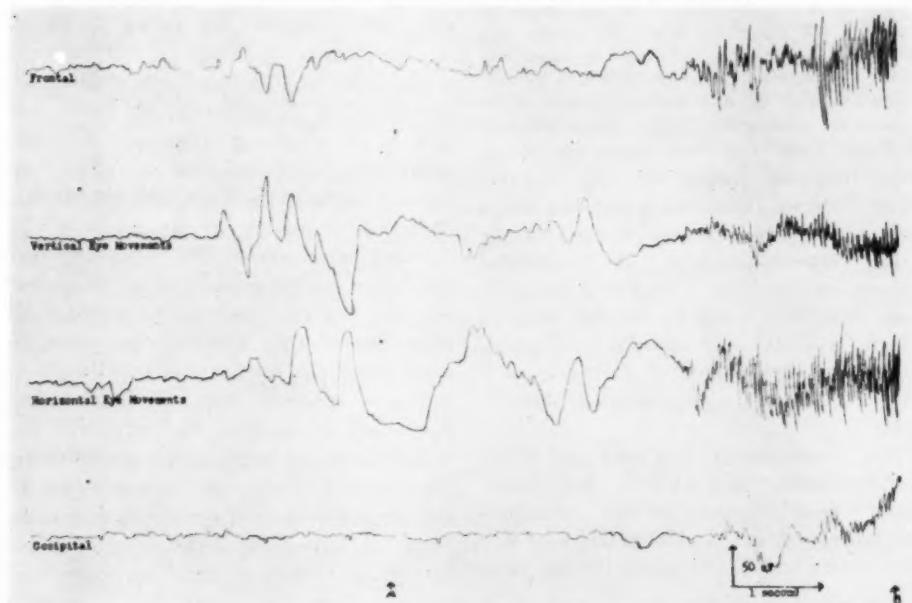
subject's usual routine was maintained as far as possible; the only restriction made was that S limit his intake of coffee and alcohol.

Two silver disc electrodes were attached to the frontal and parietal or occipital regions of the scalp with adhesive tape or with collodion. An additional four electrodes were placed about the eyes. The scalp electrodes, referred to two "indifferent" ear electrodes, record EEG patterns. Eye movements in the vertical plane are recorded by potential changes in the corneoretinal eye field picked up by the stationary supra- infraorbital electrode pair. Similar changes in the corneoretinal eye field upon horizontal movement are recorded by an electrode pair placed lateral to each eye. Gross body movements are obtained as muscle potential artifacts on all EEG leads. Lead wires from these eight electrodes and from a grounding electrode placed superior to the glabella, gathered into one bundle, are attached to the top of the scalp with collodion, and run out to an electrode box at the head of S's bed. In this manner maximal freedom of movement is permitted.

Before the start of any night's work, standardization of the potentials associated with eye movements to the left, right, up, and down was

Fig. 1.—A typical electrical recording obtained during a dreaming period of sleep. Note the low-voltage, nonspindling pattern seen in the occipital EEG lead, the high-voltage, rapid eye movements seen in the horizontal and vertical eye-movement leads, and the reduced eye-movement potentials picked up by the frontal EEG lead. In addition, muscle-potential artifact, observable in all leads, is shown to interrupt the dream period.

The arrow at A shows where S would be awakened under experimental Condition 1; the arrow at B shows where S would be awakened under experimental Condition 2.



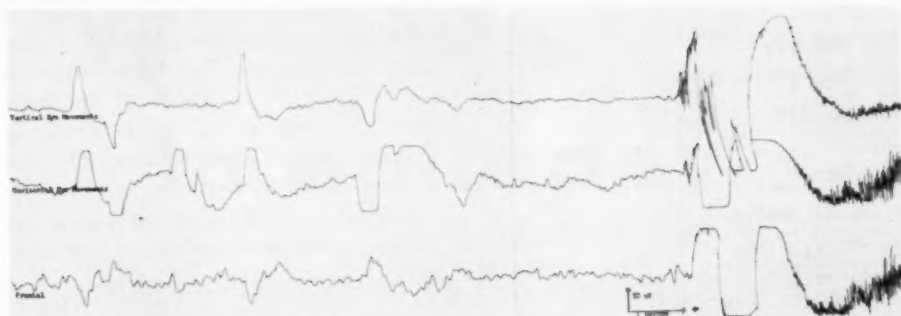


Fig. 2.—An example of an awakening made under experimental Condition 2. Shortly after the body movement began, the awakening buzzer was sounded (arrow). Note the presence of eye-movement artifact in the frontal EEG lead.

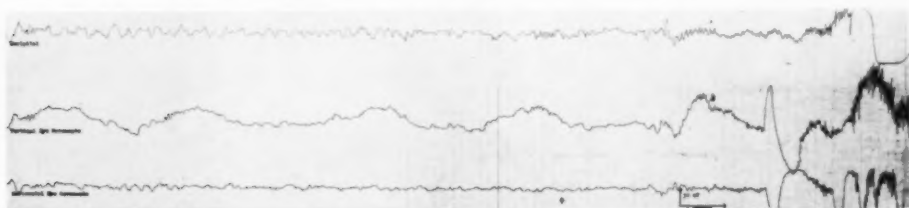


Fig. 3.—A typical awakening made during a nondreaming period of sleep (experimental Conditions 3 and 4). Note the presence of sleep spindles in the occipital EEG lead and the absence of rapid eye movements in the vertical and horizontal eye-movement leads. The buzzer was sounded at the arrow and continued until muscle-potential artifact was observed on the EEG record.

accomplished. This procedure appeared to relax our subjects and accustom them to the apparatus. Subjects slept in a quiet darkroom. Electrical potentials were amplified and recorded by a Grass Model III electroencephalograph in an adjoining room. Continuous monitoring of brain waves and eye movements at a paper speed of 0.3 cm/sec. was maintained during nondreaming periods of sleep, with a faster speed—3.0 cm/sec.—maintained during dream periods. At appropriate times S was awakened by a buzzer and asked to report his dream, if any, into a tape recorder. After S had finished his report, E elicited S's associations to the dream material. Tapes were transcribed to provide a permanent record of the dream. The evaluation of dream content will comprise the material for a later communication.

Awakenings were accomplished under four experimental conditions: (1) during an EEG pattern compatible with dreaming (Dement and Kleitman's⁶ Stage 1 of sleep; Fig. 1, *A*); (2) during a gross body movement immediately following an EEG pattern compatible with dreaming (Fig. 1, *B*; Fig. 2); (3) during an EEG pattern incompatible with dreaming (Dement and Kleitman's⁶ Stage 2 of sleep), but within 5 minutes of a pattern compatible with dreaming; (4) during

a stage of sleep incompatible with dreaming and separated from an eye movement consistent with a visual dream by at least 10 minutes (Fig. 3). The first condition represents the awakening of S in the middle of a dream episode; the second condition represents the awakening of S at the end of a dream episode, and Conditions 3 and 4 represent awakening S after his dream is over. The dream recall obtained was divided into two categories; that in which a complete drama was obtained ("detailed recall") and that in which a single scene was remembered ("fragment only").

Results and Conclusions

Table 1 reports the over-all results of this experiment, confirming previous observations that dream recall is high when awakenings are made during periods of low-voltage, nonspindling brain waves (Stage 1) and low when awakenings are made during periods of spindling brain waves (Stage 2). The data also suggest that the memory of the dream decays rapidly in time after cessation of the dream experience, and that

TABLE 1.—*Relationship of Dream Recall to Awakening Conditions*

Type of Dream Recall	During EEG Stage 1	During Gross Body Movement Interrupting EEG Stage 1	During EEG Stage 2	
			Within 5 Min. of Previous Eye Movement	After at Least 10 Min. of EEG Stage 2
(Awakenings) (Total) (214)	(54)	(123)	(11)	(26)
Detailed recall	46 (85.2%)	85 (69.1%)	--	--
Fragment only	3 (5.6)	11 (8.9)	9 (81.8%)	1 (3.8%)
No recall	5 (9.2)	27 (21.9)	2 (18.2)	25 (96.2)

dream recall becomes fragmented before undergoing complete extinction.

TABLE 2.— χ^2 Analysis of Significance of Recall Following Two Types of Awakening *

Awakening Conditions	Dream Recall	Observed in Experiment	Per Cent	Expected by Chance (1:1)	χ^2	P
During EEG Stage 1	Detailed	46	85.2	27	26.7	Less than 0.00001
	All other	8	14.8	27		
During gross body movement interrupting EEG Stage 1	Detailed	85	69.1	61.5	17.9	Less than 0.0001
	All other	38	30.8	61.5		

* 10.83 is the critical point when P equals 0.001, df equals 1.
16.00 approximates the critical point when P equals 0.0001, df equals 1.
25.00 approximates the critical point when P equals 0.00001, df equals 1.

Table 2 compares the amount of detailed dream recall obtained when Ss are awakened during the course of the nonspindling, low-voltage EEG pattern with that obtained when Ss are awakened during gross body movements interrupting such EEG patterns. While a greater percentage of dream recall is obtained in the former than in the latter case, a highly significant amount of dream recall is obtained in both cases.

Thus it appears that subjects may be awakened during gross body movements interrupting the course of a dream with the expectation that a significant amount of detailed dream recall will be obtained. Since such body movements are thought to signal a change of dream activity, the utilization of such body movements as the awakening point should allow E to obtain a maximum dream recall associated with a maximum of completed dream episodes.

Summary

EEG patterns and eye movements of 10 subjects (Ss) were monitored over 51 nights of experimental sleep. Evidence was obtained indicating that a significant amount

of dream recall may be obtained when Ss are awakened during gross body movements interrupting dreams, as well as when Ss are awakened in the middle of the dream itself. Adoption of the former awakening procedure should allow maximal elicitation of completed dream episodes.

Prof. Nathaniel Kleitman and Dr. William Dement granted permission to use their equipment.

Department of Psychiatry, The University of Chicago, 950 E. 59th St. (37) (Dr. Trosman).

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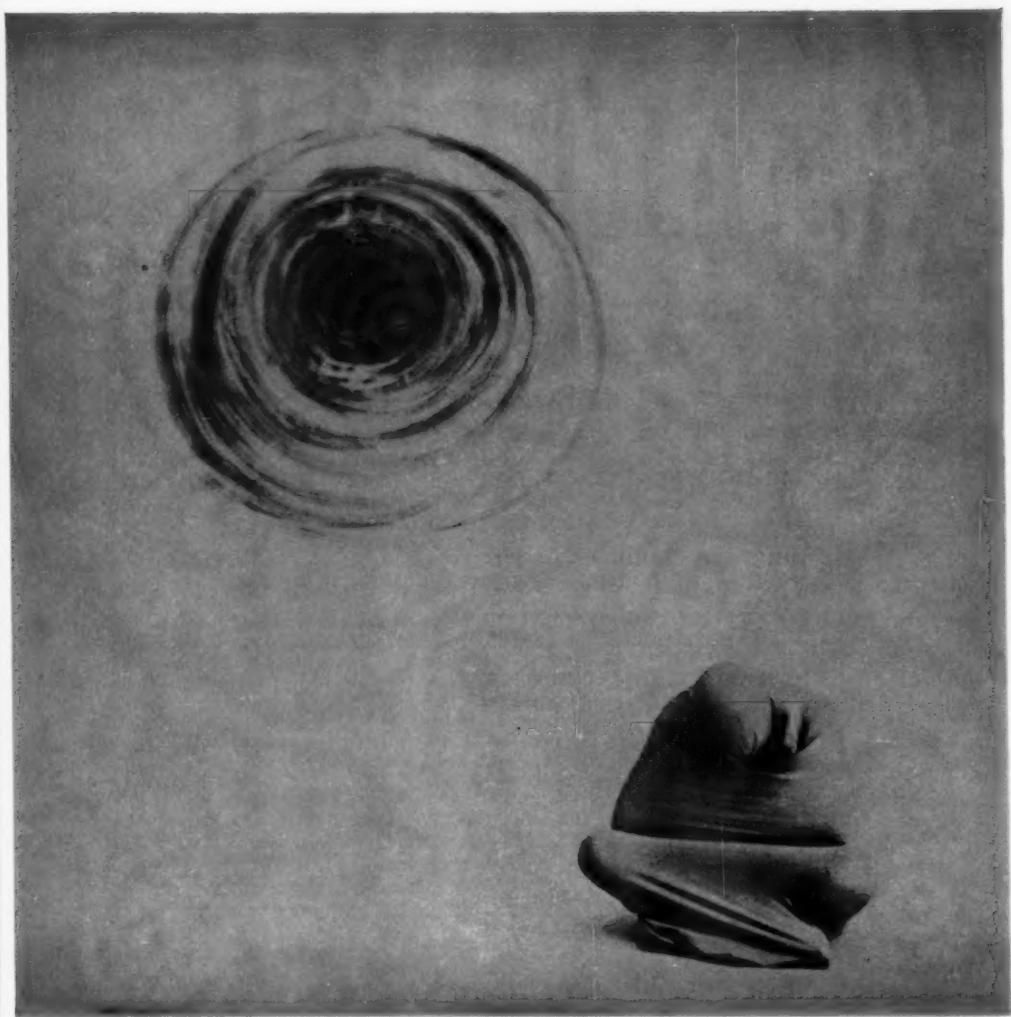
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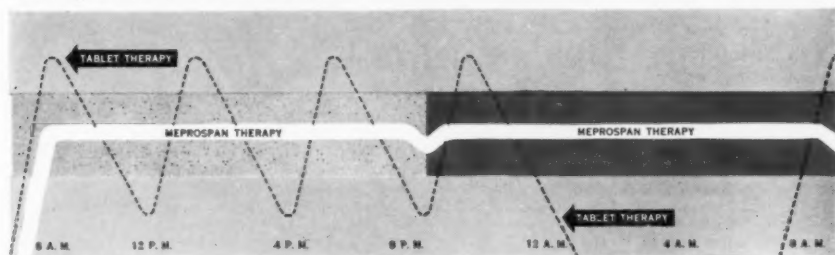
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